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UNITED STATES PATENT APPLICATION

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FOR

METHOD OF USING AMINOCYANOPYRIDINE COMPOUNDS AS MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2 INHIBITORS

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METHOD OF USING AMINOCYANOPYRIDINE COMPOUNDS AS MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2 INHIBITORS

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/432,807, filed December 12, 2002, which is incorporated herein by reference in its entirety. This application is related to commonly assigned and copending applications having the titles "Method of making tricyclic aminocyanopyridine compounds" (and having Provisional Application Serial No. 60/432,783), "Tricyclic aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase-2" (and having Provisional Application Serial No. 60/432,844), and "Aminocyanopyridine inhibitors of mitogen activated protein kinase-activated protein kinase-2" (and having Provisional Application Serial No. 60/432,843), each of which was filed on the same date as the present application.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to a method of inhibiting mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2, or MK-2) in a subject in need of such inhibition, and also to the prevention and treatment of TNFα mediated diseases or disorders by the administration of an MK-2 inhibitor.

(2) Description of the Related Art:

[0003] Mitogen-activated protein kinases (MAPKs) are members of conserved signal transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. MAPKs are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr by mitogen-activated protein kinase kinases (MAPKKs). In higher eukaryotes, the physiological role of MAPK signaling has been correlated with cellular events such as

proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

[0004] In mammalian cells, three parallel MAPK pathways have been described. The best characterized pathway leads to the activation of the extracellular-signal-regulated kinase (ERK). Less well understood are the signal transduction pathways leading to the activation of the cJun N-terminal kinase (JNK) and the p38 MAPK. See, *e.g.*, Davis, *Trends Biochem. Sci. 19*:470-473 (1994); Cano, *et al., Trends Biochem. Sci. 20*:117-122(1995).

[0005] The p38 MAPK pathway is potentially activated by a wide variety of stresses and cellular insults. These stresses and cellular insults include heat shock, UV irradiation, inflammatory cytokines (such as TNF and IL-1), tunicamycin, chemotherapeutic drugs (*i.e.*, cisplatinum), anisomycin, sorbitol/hyperosmolarity, gamma irradiation, sodium arsenite, and ischaemia. See, Ono, K., *et al, Cellular Signalling 12*, 1 - 13 (2000). Activation of the p38 pathway is involved in (1) production of proinflammatory cytokines, such as TNF-α; (2) induction of enzymes, such as Cox-2; (3) expression of an intracellular enzyme, such as iNOS, which plays an important role in the regulation of oxidation; (4) induction of adherent proteins, such as VCAM-1 and many other inflammatory-related molecules. Furthermore, the p38 pathway functions as a regulator in the proliferation and differentiation of cells of the immune system. See, Ono, K., *et al., Id.* at 7.

[0006] The p38 kinase is an upstream kinase of mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2 or MK-2). (See, Freshney, N. W., *et al., J. Cell, 78*:1039-1049 (1994)). MK-2 is a protein that appears to be predominantly regulated by p38 in cells. Indeed, MK-2 was the first substrate of p38α to be identified. For example, *in vitro* phosphorylation of MK-2 by p38α activates MK-2. The

substrates that MK-2 acts upon, in turn, include heat shock protein 27, lymphocyte-specific protein 1 (LAP1), cAMP response element-binding protein (CREB), ATF1, serum response factor (SRF), and tyrosine hydroxylase. The substrate of MK-2 that has been best characterized is small heat shock protein 27 (hsp27).

[0007] The role of the p38 pathway in inflammatory-related diseases has been studied in several animal models. The pyridinyl imidazole compound SB203580 has been shown to be a specific inhibitor of p38 *in vivo,* and also has been shown to inhibit activation of MK-2, (See, Rouse, J., *et al, Cell, 78*:1027-1037 (1994); Cuenda, A., *et al, Biochem. J., 333*:11-15 (1998)), as well as a MAP kinase homologue termed reactivating kinase (RK). (See, Cuenda, A., *et al., FEBS Lett., 364(2)*:229 - 233 (1995)). Inhibition of p38 by SB203580 can reduce mortality in a murine model of endotoxin-induced shock and inhibit the development of mouse collagen-induced arthritis and rat adjuvant arthritis. See, *e.g.,* Badger, A. M., *et al., J. Pharmacol Exp. Ther., 279*:1453 - 1461 (1996). Another p38 inhibitor that has been utilized in an animal model that is believed to be more potent than SB203580 in its inhibitory effect on p38 is SB 220025. A recent animal study has demonstrated that SB 220025 caused a significant dose-dependent decrease in vascular density of granulomas in laboratory rats. (See Jackson, J. R., *et al, J. Pharmacol. Exp. Ther., 284*:687 - 692 (1998)). The results of these animal studies indicated that p38, or the components of the p38 pathway, can be useful therapeutic targets for the prevention or treatment of inflammatory disease.

[0008] Due to its integral role in the p38 signaling pathway, MK-2 has been used as a monitor for measuring the level of activation in the pathway. Because of its downstream location in the pathway, relative to p38, MK-2 has been measured as a more convenient, albeit indirect, method of assessing p38 activation. However, so far, research efforts exploring therapeutic strategies associated with the modulation of this pathway have focused mainly on the inhibition of p38 kinase.

[0009] Several compounds that inhibit the activity of p38 kinase have been described in U.S. Patent Nos. 6,046,208, 6,251,914, and 6,335,340. These compounds have been suggested to be useful for the treatment of CSBP/RK/p38 kinase mediated disease. Commercial efforts to apply p38 inhibitors have centered around two p38 inhibitors, the pyridinylimidazole inhibitor SKF 86002, and the 2,4,5 triaryl imidazole inhibitor SB203580. See, Lee, J. C., *et al, Immunopharmacology 47,* 185-192 (2000). Compounds possessing a similar structure have also been investigated as potential p38 inhibitors. Indeed, p38 MSP kinase's role in various disease states has been elucidated through the use of inhibitors.

[00010] Kotlyarov, A. *et al,* in *Nat. Cell Biol., 1(2)*:94 - 97 (1999) introduced a targeted mutation into a mouse MK-2 gene, resulting in MK-2-deficient mice. It was shown that mice lacking MK-2 possessed increased stress resistance and survived LPS-induced endotoxic shock better than MK-2^+ mice. The authors concluded that MK-2 was an essential component in the inflammatory response that regulates biosynthesis of TNFα at a post-transcriptional level. More recently, Lehner, M.D., *et al,* in *J. Immunol., 168(9)*:4667-4673 (2002), reported that MK-2-deficient mice showed increased susceptibility to *Listeria monocytogenes* infection, and concluded that MK-2 had an essential role in host defense against intracellular bacteria, probably via regulation of TNF and IFN-gamma production required for activation of antibacterial effector mechanisms.

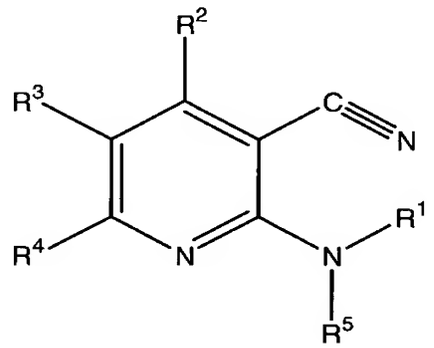
[00011] The location of MK-2 in the p38 signaling pathway at a point that is downstream of p38 offers the potential that MK-2 could act as a focal point for modulating the pathway without affecting as many substrates as would the regulation of an enzyme further upstream in the signaling cascade -- such as p38 MAP kinase.

[00012] Accordingly, it would be useful to provide compounds and methods that could serve to modulate the activity of MK-2 -- in particular, to act as inhibitors of MK-2 activity. Such compounds and methods would be useful for the provision of benefits similar to p38 MAP kinase inhibitors,

which benefits include the prevention and treatment of diseases and disorders that are mediated by TNFα. It would be even more useful to provide MK-2 inhibitors having improved potency and reduced undesirable side effects, relative to p38 inhibitors.

SUMMARY OF THE INVENTION

[00013] Briefly, therefore the present invention is directed to a novel method of inhibiting mitogen activated protein kinase-activated protein kinase-2 in a subject in need of such inhibition, the method comprising administering to the subject an anminocyanopyridine MK-2 inhibiting compound, or a pharmaceutically acceptable salt thereof, the compound having the structure:

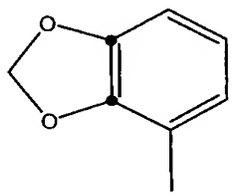


wherein:

R^1 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, carboxy C_1-C_4 alkyl, aryl C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylamino, C_1-C_4 alkyl, di-(C_1-C_4 alkyl)amino C_1-C_4 alkyl, C_1-C_4 alkyl-C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, and aryl C_1-C_4 alkylcarbonyl;

R^2 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino, amino C_1-C_4 alkyl, C_1-C_4 alkylamino, aryl, heteroaryl, heterocyclyl, carboxy, carboxy C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkylamino, hydroxy C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkoxy C_1-C_4 alkylamino, amino C_1-C_4 alkylamino, aryl C_1-C_4 alkyl, C_1-C_4 alkylamino C_1-C_4 alkyl, di C_1-C_4

alkylamino C_1-C_4 alkyl, C_1-C_4 alkyl C_1-C_4 alkyl, carboxy C_1-C_4 alkyl, aryl C_1-C_4 alkylcarbonyl, phthaloamino C_1-C_4 alkyl, halo, carbamyl, C_1-C_4 alkylthio, C_1-C_4 alkoxyarylamino, C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl can be optionally substituted with one or more of the groups selected from halogen, hydroxy, C_1-C_4 alkoxy, aryloxy, C_2-C_4 alkenyloxy, C_2-C_4 alkynyloxy, C_1-C_4 alkyl, carboxy, carbamyl, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl C_1-C_4 alkoxy, carboxy C_1-C_4 alkoxy amino, C_1-C_4 alkylamino, di-C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy,



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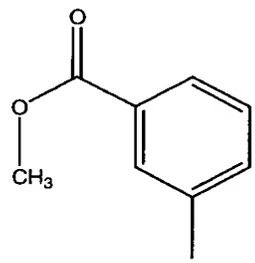
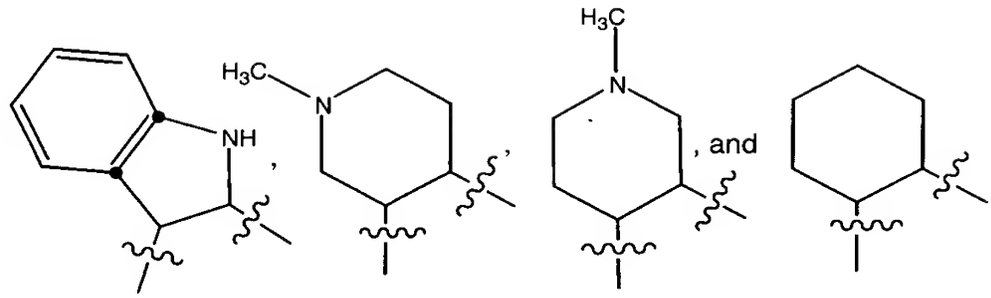


;

R^3 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, amino C_1-C_4 alkyl, amino, aryl, wherein the aryl group optionally can be substituted with one or more group selected from halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, carboxy, C_1-C_4 alkoxycarbonyl, carboxy C_1-C_4 alkoxy, amino, di- C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, di-halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy, and

where the R^2 and R^3 groups are such that they optionally join to form a ring system selected from:



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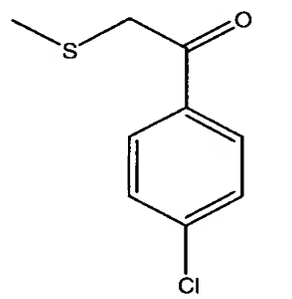
R^4 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_4 alkylthio, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, mercapto, *N*-imidazoylphenyl, , C_1-C_4 isoalkyl, aminofluorobenzhydryl, aryl and heteroaryl, wherein the aryl and heteroaryl groups optionally can be substituted with one or more groups selected from halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl, cartoxy, carbamyl, C_1-C_4 alkoxycarbonyl, carboxy C_1-C_4 alkyl, carboxy C_1-C_4 alkoxy, amino, di- C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, di-halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy



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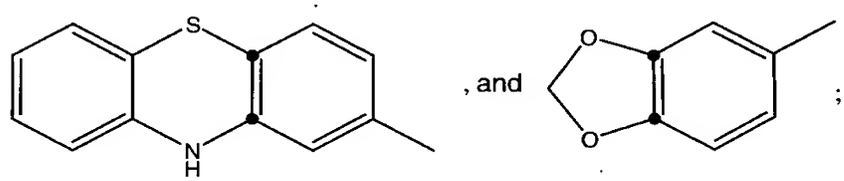

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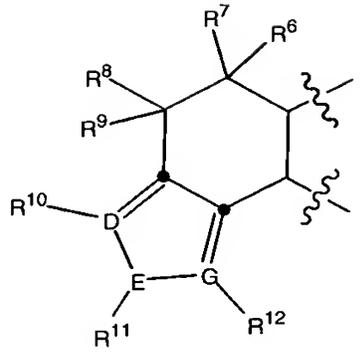
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from:


R7
R6
R8
R9
R10
D
E
G
R11
R12

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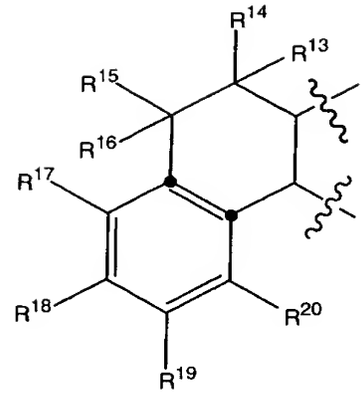
R14
R13
R15
R16
R17
R18
R20
R19

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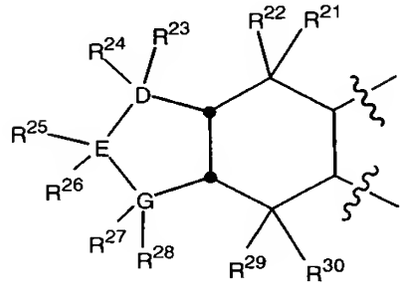
R22
R21
R24
R23
D
R25
E
R26
G
R27
R28
R29
R30

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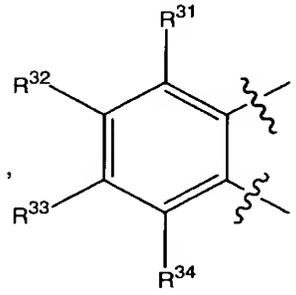
R31
R32
R33
R34

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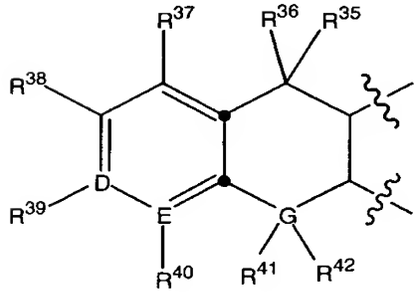
R37
R36
R35
R38
D
R39
E
G
R40
R41
R42

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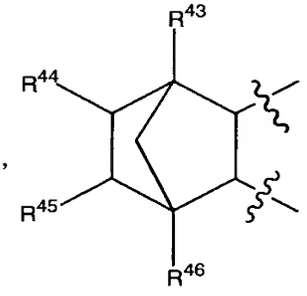
R43
R44
R45
R46

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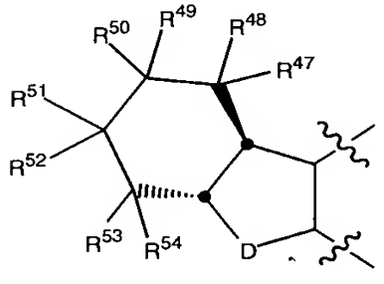
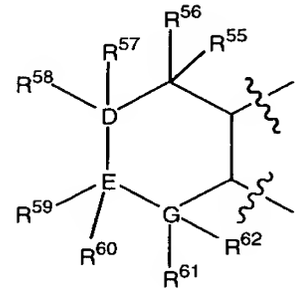

R50
R49
R48
R47
R51
R52
R53
R54
D

,


R56
R57
R55
R58
D
E
R59
G
R62
R60
R61

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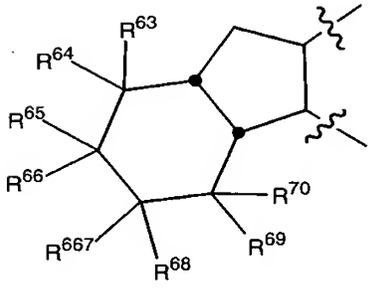
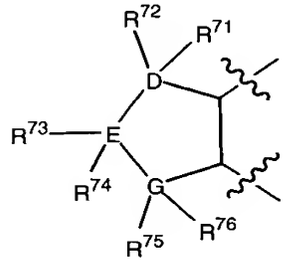

R63
R64
R65
R66
R667
R68
R70
R69

, and


R72
R71
D
R73
E
R74
G
R75
R76

;

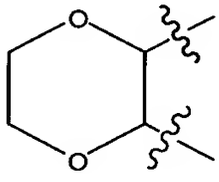
D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

R^5 is selected from the group consisting of -H, and C_1-C_5 alkyl; and

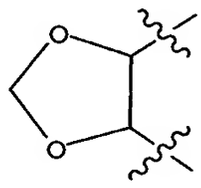
wherein the R^1 and R^5 groups optionally join to form a piperidyl ring or oxazinyl ring;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present and are each independently selected from the group consisting of -H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 isoalkyl, amino, nitro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkenoxy, oxo, carboxy, halo, halo C_1-C_4 alkyl, dihalo C_1-C_4 alkyl, trihalo C_1-C_4 alkyl, cyano, cyano C_1-C_4 alkyl, dicyano C_1-C_4 alkyl, halophenyl, hydroxy C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkoxy, -(CH_2)-O-(C_6H_4)-O-(CH_3), carboxy C_1-C_4 alkoxy, C_1-C_4 alkylcarboxy C_1-C_4 alkoxy, C_1-C_4 alkoxyamino, C_1-C_4 alkylamino, di C_1-C_4 alkylamino, tri C_1-C_4 alkylamino, amino C_1-C_4 alkoxy, diamino C_1-C_4 alkoxy, C_1-C_4 alkylamino C_1-C_4 alkoxy, di C_1-C_4 alkylamino C_1-C_4 alkoxy, cyano C_1-C_4 alkoxy C_1-C_4 alkyl, -(CH_2)-O-(CF_2)-CHF_2, tetra C_1-C_4 alkoxy C_1-C_4 alkyl, phenyl, benzyl, benzoyl, aryl, *N*-morpholinyl, morpholinyl C_1-C_4 alkoxy, pyrrolidyl C_1-C_4 alkoxy, *N*-pyrrolidyl C_1-C_4 alkoxy, C_1-C_4 alkylcarboxy, carboxy C_1-C_4 alkyl - ethyl ester, pyridyl C_1-C_4 alkyl, pyridyl C_1-C_4 alkoxy, -COO-CH_2-CH_3; and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from:



, and



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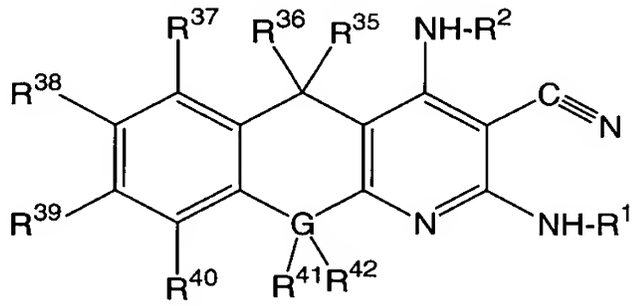
[00014] The invention is also direct to a novel method of inhibiting mitogen activated protein kinase-activated protein kinase-2 in a subject in need of such inhibition, the method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, the compound having the structure:



wherein:

G is selected from the group consisting of - O -, - S -, and -N-;

when G is -O-, R^{41} and R^{42} are absent;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -N-, R^{41} is absent, and R^{42} is -H or C_1-C_4-alkyl;

R^1, R^2, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, and R^{40} each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_2-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy

C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

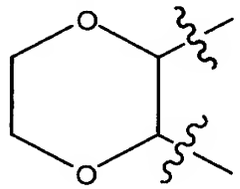
aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

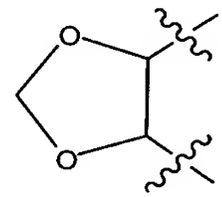
branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from



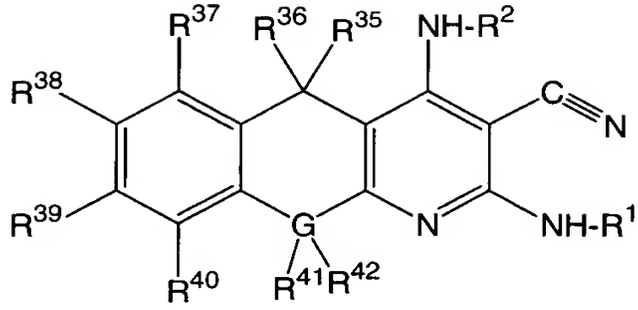
, and



.

[00015] In preferred embodiments, R^{38} is other than cyano.

[00016] The present invention is also directed to a novel method of inhibiting mitogen activated protein kinase-activated protein kinase-2 in a subject in need of such inhibition, the method comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, the compound having the structure:



wherein:

G is selected from the group consisting of -O-, -S-, and -N-;

when G is -O-, R^{41} and R^{42} are absent;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -N-, R^{41} is absent , and R^{42} is -H or $-CH_3$;

R^1 is selected from the group consisting of hydrogen, ethyl, dimethylaminoethyl, butyl, propyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^2 is selected from the group consisting of hydrogen, hydroxyethyl, propyl, ethyl, methyl, 4-methoxyphenyl, ethoxyethyl, aminoethyl, phenylmethyl, dimethylaminoethyl, phthaloaminoethyl, butyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^{35} is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl.

R^{36} is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl;

R^{37} is selected from the group consisting of hydrogen, hydroxy, methoxy, bromo, and 2-pyridomethyl;

R^{38} is selected from the group consisting of hydrogen, hydroxy, methoxy, amino, carboxy, diaminoethoxy, bromo, propoxy, isobutylcarboxymethoxy, dimethylamino, nitro, phenyl, chloro, pyridylmethyl, and fluoro;

R^{39} is selected from the group consisting of hydrogen, hydroxy, methoxy, hydroxyethoxy, ethoxyethoxy, ethoxy, aminoethoxy, morpholinoethoxy, carboxymethoxy, *N*-pyrrolidylethoxy, dimethylaminoethoxy, pyridylmethyl, 2-propenoxy, and

isobutylcarboxymethoxy, where the R^{38} and R^{39} groups can join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, fluoro, methoxy, nitro, amino, pyrrolidylethoxy, carboxymethoxy, methyl, hydroxyethoxy, aminoethoxy, 4-pyridylmethoxy, isobutyl, ethylcarboxy, dimethylaminoethoxy, carboxy, bromo, and pyrridylmethyl.

[00017] The present invention is also directed to a novel method of preventing or treating a TNFα mediated disease or disorder in a subject in need of such prevention or treatment, the method comprising administering to the subject an effective amount of an aminocyanopyridine MK-1 inhibiting compound.

[00018] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of a method that could serve to modulate the activity of MK-2 -- in particular, to inhibit MK-2 activity, and the provision of a method for the prevention and treatment of diseases and disorders that are mediated by TNFα.

BRIEF DESCRIPTION OF THE DRAWINGS

[00019] Figure 1 is a graph showing paw thickness as a function of time from day 0 to day 7 for MK2 (+/+) and MK2 (-/-) mice, which have received serum injection; and

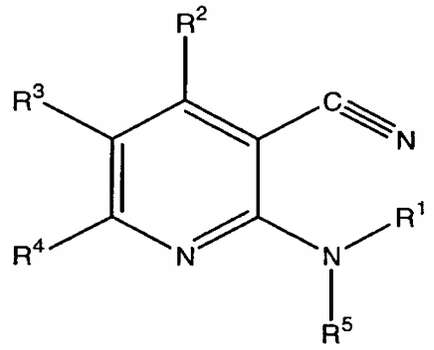
[00020] Figure 2 is a bar chart showing paw thickness at seven days after injection for normal mice, MK2 (+/+) mice receiving serum, MK2 (-/-) mice receiving serum, and MK2 (+/+) mice receiving serum and anti-TNF antibody.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00021] In accordance with the present invention, it has been discovered that certain aminocyanopyridine compounds can inhibit the activity of MAPKAP kinase-2. Many of these compounds exhibit their inhibitory effect at low concentrations -- having *in vitro* MK-2 inhibition IC_{50} values of under 1.0 μM, and with some having IC_{50} values of under about 0.5 μM, and even as low as about 0.2 μM. Accordingly, these compounds can be potent and effective drugs for use in methods to prevent or treat

diseases and disorders that are mediated by TNFα. For example, they can be used for the prevention or treatment of arthritis.

[00022] Aminocyanopyridine compounds that are useful in the present method include those having the structure shown in formula I:



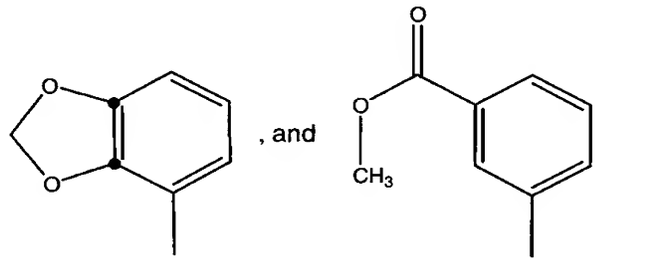
I

wherein:

R^1 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, carboxy C_1-C_4 alkyl, aryl C_1-C_4 alkyl, amino, amino C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylamino, C_1-C_4 alkyl, di-(C_1-C_4 alkyl)amino C_1-C_4 alkyl, C_1-C_4 alkyl-C_1-C_4 alkyl, hydroxy C_1-C_4 alkyl, and aryl C_1-C_4 alkylcarbonyl;

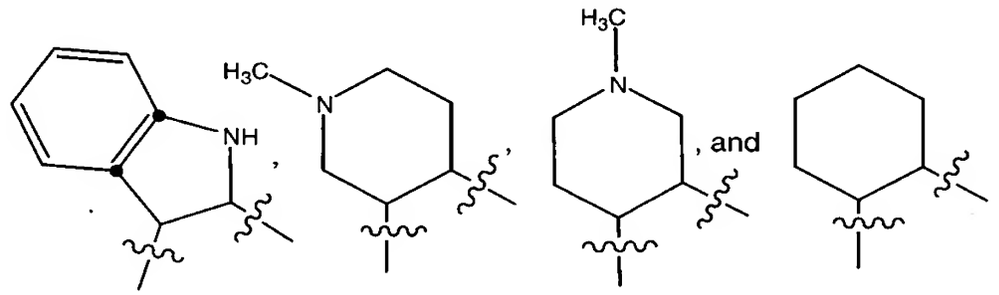
R^2 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, amino, amino C_1-C_4 alkyl, C_1-C_4 alkylamino, aryl, heteroaryl, heterocyclyl, carboxy, carboxy C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, hydroxy C_1-C_4 alkyl, hydroxy C_1-C_4 alkylamino, hydroxy C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkyl, C_1-C_4 alkoxy C_1-C_4 alkylamino, amino C_1-C_4 alkylamino, aryl C_1-C_4 alkyl, C_1-C_4 alkylamino C_1-C_4 alkyl, di C_1-C_4 alkylamino C_1-C_4 alkyl, C_1-C_4 alkyl C_1-C_4 alkyl, carboxy C_1-C_4 alkyl, aryl C_1-C_4 alkylcarbonyl, phthaloamino C_1-C_4 alkyl, halo, carbamyl, C_1-C_4 alkylthio, C_1-C_4 alkoxyarylamino, C_1-C_{10} mono- and bicyclic cycloalkyl, wherein aryl, heteroaryl, heterocyclyl, mono- and bicyclic cycloalkyl can be optionally substituted with one or more of the groups selected from halogen, hydroxy, C_1-C_4 alkoxy, aryloxy, C_2-C_4 alkenyloxy, C_2-C_4 alkynyloxy, C_1-C_4 alkyl, carboxy, carbamyl, C_1-C_4 alkoxycarbonyl, C_1-C_4

alkoxycarbonyl C_1-C_4 alkoxy, carboxy C_1-C_4 alkoxy amino, C_1-C_4 alkylamino, di-C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, hydroxy C_1-C_4 alkoxy, halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy,



R^3 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cyano, amino C_1-C_4 alkyl, amino, aryl, wherein the aryl group optionally can be substituted with one or more group selected from halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, carboxy, C_1-C_4 alkoxycarbonyl, carboxy C_1-C_4 alkoxy, amino, di- C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, di-halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy, and

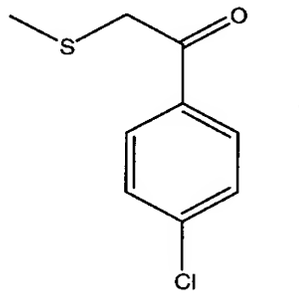
where the R^2 and R^3 groups are such that they optionally join to form a ring system selected from:



[00023] As shown above, ring substituent groups that join to form additional ring structures adjacent the substituted ring can be described with reference to chemical formulas that show wavy lines to indicate that a

partial molecule is shown. In these formulas, the wavy lines cut through the ring to which the substituents are joined (in this case, the pyridine ring of formula I), rather than across the bond joining the substituent group to the ring. Accordingly, the partial ring that is shown is the ring to which the substituent groups are shown as being bonded in the general formula.

R^4 is selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_4 alkylthio, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, mercapto, *N*-imidazoylphenyl, , C_1-C_4 isoalkyl, aminofluorobenzhydryl, aryl and heteroaryl, wherein the aryl and heteroaryl groups optionally can be substituted with one or more groups selected from halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl, cartoxy, carbamyl, C_1-C_4 alkoxycarbonyl, carboxy C_1-C_4 alkyl, carboxy C_1-C_4 alkoxy, amino, di- C_1-C_4 alkylamino, *N*-C_1-C_4 alkyl-*N*-cyano C_1-C_4 alkylamino, nitro, C_1-C_4 alkylcarbonylamino, cyano, halo C_1-C_4 alkyl, di-halo C_1-C_4 alkyl, tri-halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, di-halo C_1-C_4 alkoxy, tri-halo C_1-C_4 alkoxy



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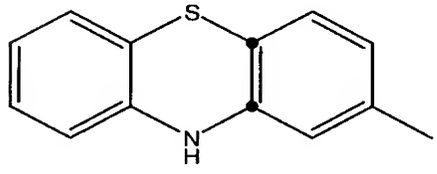

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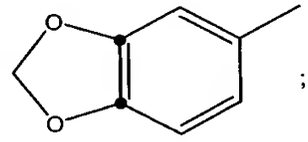
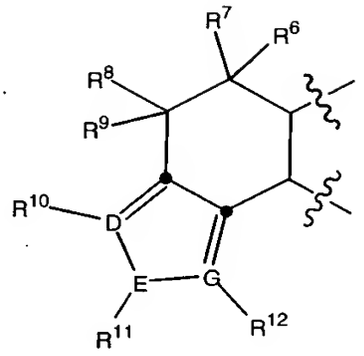
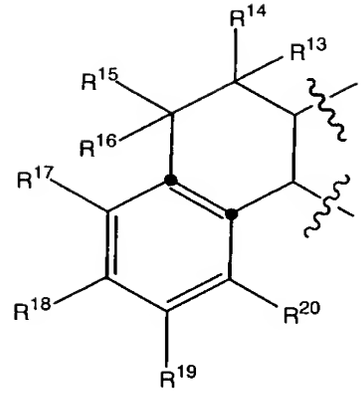


;

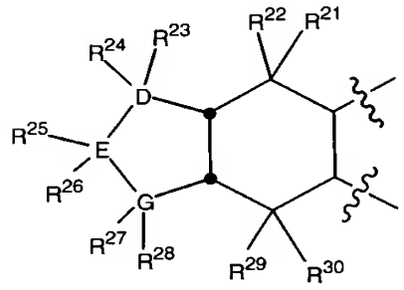
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from:


R7
R6
R8
R9
R10
D
E
G
R11
R12

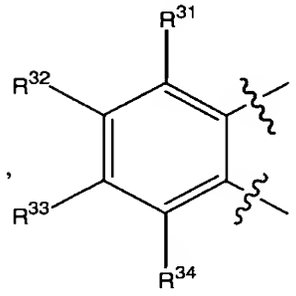
,


R14
R13
R15
R16
R17
R18
R19
R20

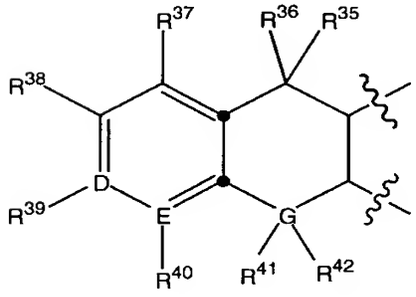
,


R22
R21
R24
R23
D
R25
E
R26
G
R27
R28
R29
R30

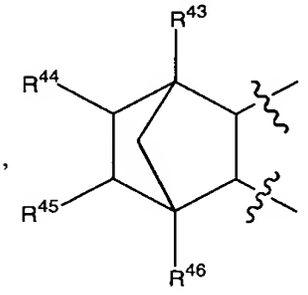
,


R31
R32
R33
R34

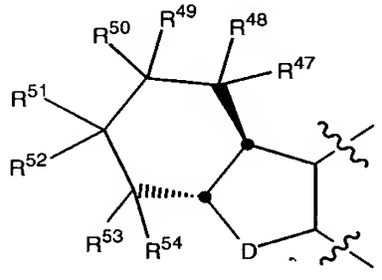
,


R37
R36
R35
R38
D
R39
E
G
R40
R41
R42

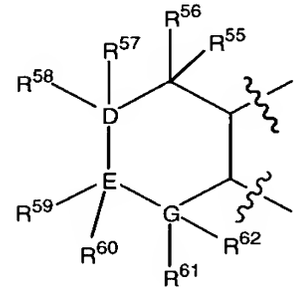
,


R43
R44
R45
R46

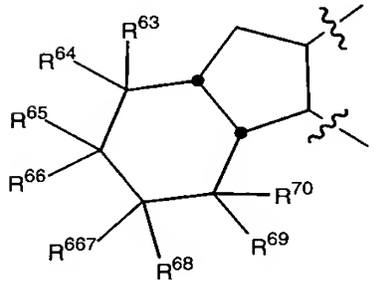
,


R50
R49
R48
R47
R51
R52
R53
R54
D

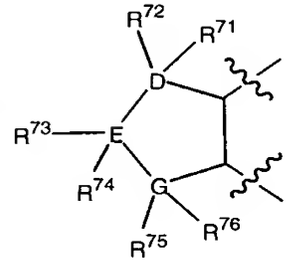
,


R56
R57
R55
R58
D
E
R59
G
R60
R62
R61

,


R63
R64
R65
R66
R667
R68
R69
R70

, and


R72
R71
D
R73
E
R74
G
R75
R76

;

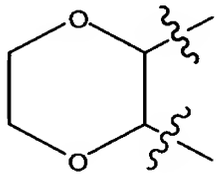
D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

R^5 is selected from the group consisting of -H, and C_1-C_5 alkyl; and

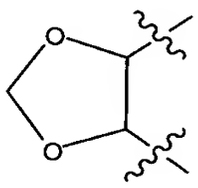
wherein the R^1 and R^5 groups can join to form a piperidyl ring or an oxazinyl ring;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present and are each independently selected from the group consisting of -H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 isoalkyl, amino, nitro, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkenoxy, oxo, carboxy, halo, halo C_1-C_4 alkyl, dihalo C_1-C_4 alkyl, trihalo C_1-C_4 alkyl, cyano, cyano C_1-C_4 alkyl, dicyano C_1-C_4 alkyl, halophenyl, hydroxy C_1-C_4 alkoxy, C_1-C_4 alkoxy C_1-C_4 alkoxy, -(CH_2)-O-(C_6H_4)-O-(CH_3), carboxy C_1-C_4 alkoxy, C_1-C_4 alkylcarboxy C_1-C_4 alkoxy, C_1-C_4 alkoxyamino, C_1-C_4 alkylamino, di C_1-C_4 alkylamino, tri C_1-C_4 alkylamino, amino C_1-C_4 alkoxy, diamino C_1-C_4 alkoxy, C_1-C_4 alkylamino C_1-C_4 alkoxy, di C_1-C_4 alkylamino C_1-C_4 alkoxy, cyano C_1-C_4 alkoxy C_1-C_4 alkyl, -(CH_2)-O-(CF_2)-CHF_2, tetra C_1-C_4 alkoxy C_1-C_4 alkyl, phenyl, benzyl, benzoyl, aryl, *N*-morpholinyl, morpholinyl C_1-C_4 alkoxy, pyrrolidyl C_1-C_4 alkoxy, *N*-pyrrolidyl C_1-C_4 alkoxy, C_1-C_4 alkylcarboxy, carboxy C_1-C_4 alkyl - ethyl ester, pyridyl C_1-C_4 alkyl, pyridyl C_1-C_4 alkoxy, -COO-CH_2-CH_3; and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from:



, and



.

[00024] In a preferred embodiment, when R^2 is heteroaryl, R^3 is other than cyano.

[00025] It is also preferred that at least one of R^1, R^2, R^3, R^4, and R^5 is other than hydrogen.

[00026] In another embodiment, when R^1, R^3 and R^5 are hydrogen:

R^2 is other than alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocyclealkyl, heterocyclealkylcarbonyl, (NZ_1Z_2)alkyl, or $-R_AR_B$;

where Z_1 and Z_2 are each independently selected from the group consisting of hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, benzyl, benzyloxycarbonyl, and formyl;

R^A is selected from the group consisting of aryl and arylalkyl;

R^B is selected from the group consisting of aryl, arylalkoxy, arylalkyl, aryloxy, heterocycle, and heterocyclealkyl; and

R^4 is other than alkenyl, alkoxyalkynyl, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocycle, heterocyclealkyl, or $-R_CR_DR_E$;

where R_C is selected from the group consisting of aryl, arylalkyl, heterocycle and heterocyclealkyl;

R_D is selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl; and

R_E is absent or selected from the group consisting of aryl, arylalkoxy, arylalkoxyimino, arylalkyl, aryloxy, heterocycle, heterocyclealkoxy, heterocyclealkyl, heterocyclecarbonyl, heterocycleimino, heterocycleoxy, heterocycleoxyalkyl, heterocycleoxyimino, heterocycleoxyiminoalkyl, and heterocyclesulfonyl.

[00027] As used herein, the term "alkyl", alone or in combination, means an acyclic alkyl radical, linear or branched, which, unless otherwise noted, preferably contains from 1 to about 10 carbon atoms and more preferably contains from 1 to about 6 carbon atoms. "Alkyl" also

encompasses cyclic alkyl radicals containing from 3 to about 7 carbon atoms, preferably from 3 to 5 carbon atoms. The alkyl radicals can be optionally substituted with groups as defined below. Examples of such alkyl radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl, and the like.

[00028] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[00029] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00030] The term "alkoxy" includes linear or branched oxy-containing radicals, each of which has, unless otherwise noted, alkyl portions of 1 to about 6 carbon atoms, preferably 1 to about 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, isobutoxy radicals, and the like.

[00031] The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Examples of such radicals

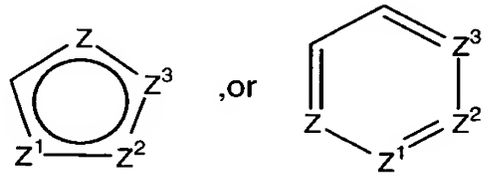
include methoxyalkyls, ethoxyalkyls, propoxyalkyls, isopropoxyalkyls, butoxyalkyls, tert-butoxyalkyls, and the like. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" radicals. Examples of such radicals includ fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, fluoropropoxy, and the like.

[00032] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, preferably, unless otherwise noted, of from 1 to about 6 carbon atoms, attached to a divalent sulfur atom. An example of "lower alkylthio", is methylthio (CH_3-S-).

[00033] The term "alkylthioalkyl" embraces alkylthio radicals, attached to an alkyl group. An example of such radicals is methylthiomethyl.

[00034] The term "halo" means radicals comprising halogens, such as fluorine, chlorine, bromine, or iodine.

[00035] The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

[00036] The term "heteroaryl" means a fully unsaturated heterocycle, which can include, but is not limited to, furyl, thenyl, pyrryl, imidazolyl, pyrazolyl, pyridyl, thiazolyl, quinolinyl, isoquinolinyl, benzothienyl, and indolyl.

[00037] In either, "heterocyclyl" or "heteroaryl", the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

[00038] The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to about seven carbon atoms, preferably three to about six carbon atoms, and more preferably three to about five carbon atoms. Examples include radicals, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepine.

[00039] The term "oxo" means a doubly-bonded oxygen.

[00040] The term "aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

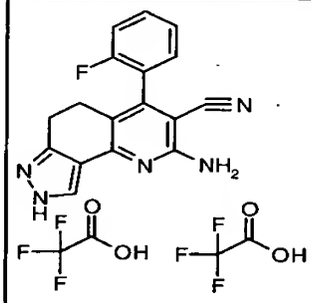
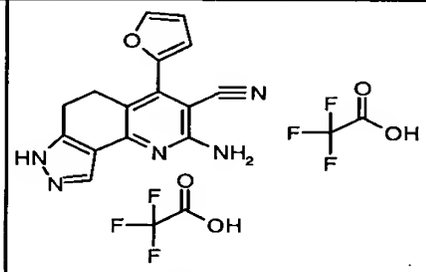
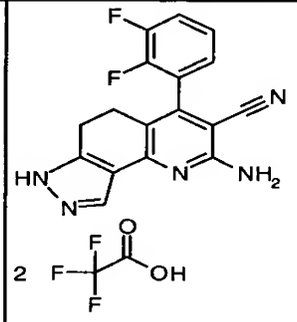
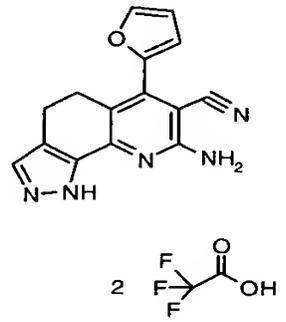
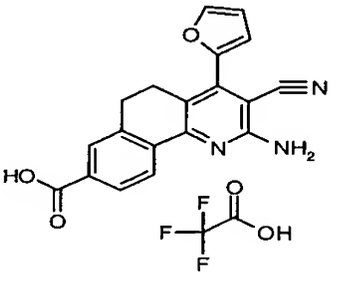
[00041] The present aminocyanopyridine compounds inhibit the activity of the MK-2 enzyme. When it is said that a subject compound inhibits MK-2, it is meant that the MK-2 enzymatic activity is lower in the presence of the compound than it is under the same conditions in the absence of such compound.

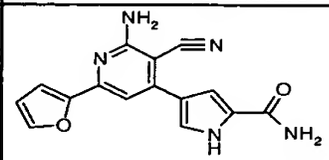
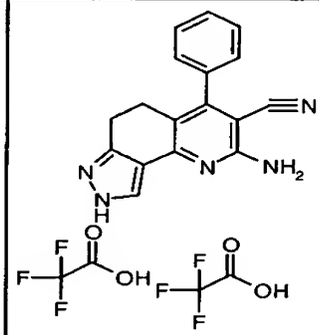
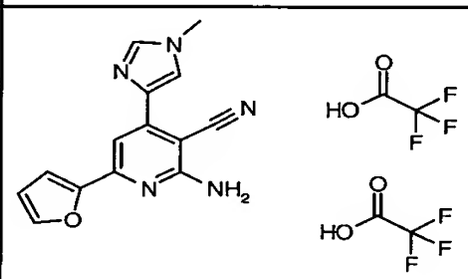
[00042] One method of expressing the potency of a compound as an MK-2 inhibitor is to measure the "IC_{50}" value of the compound. The IC_{50} value of an MK-2 inhibitor is the concentration of the compound that is required to decrease the MK-2 enzymatic activity by one-half. Accordingly, a compound having a lower IC_{50} value is considered to be a more potent inhibitor than a compound having a higher IC_{50} value. As used herein, aminocyanopyridine compounds that inhibit MK-2 can be

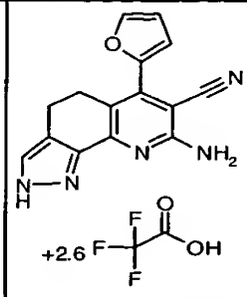
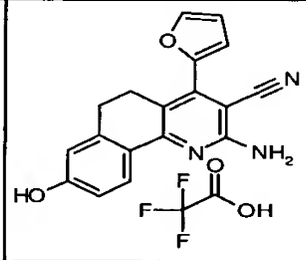
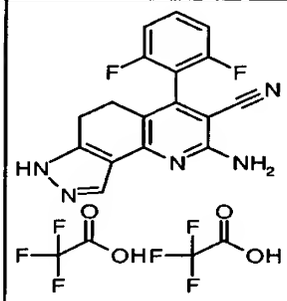
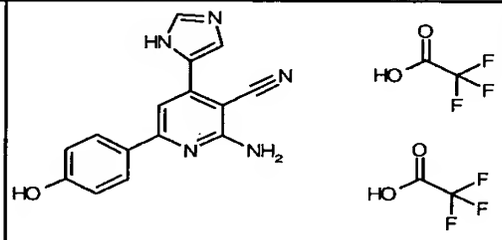
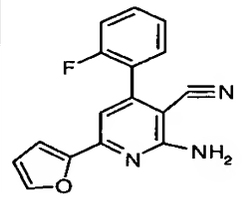
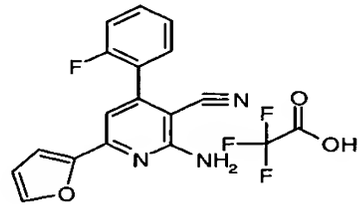
referred to as aminocyanopyridine MK-2 inhibitors, or aminocyanopyridine MK-2 inhibiting compounds or MK-2 inhibiting agents.

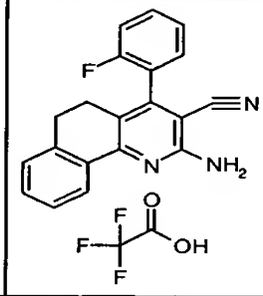
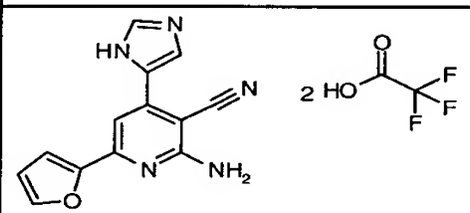
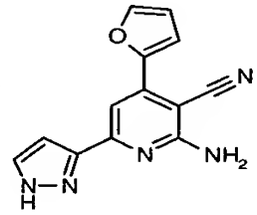
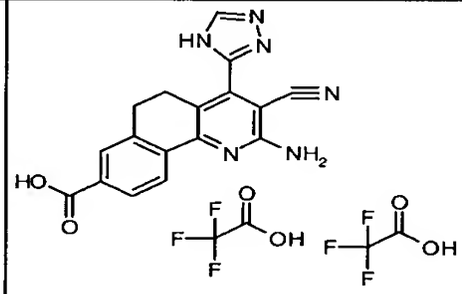
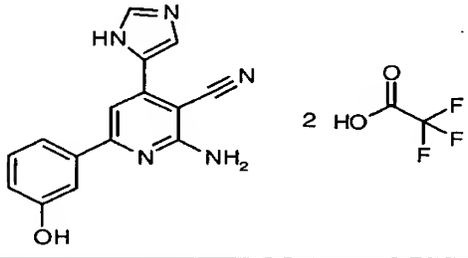
[00043] Examples of aminocyanopyridine compounds that are suitable for use as MK-2 inhibitors in the present invention are shown in Table I.

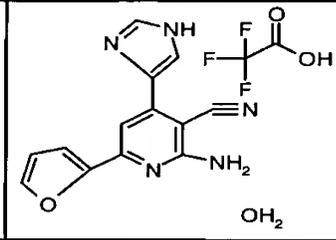
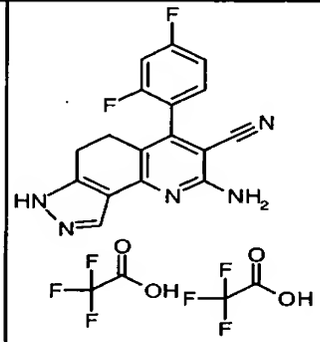
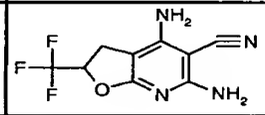
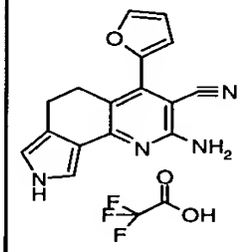
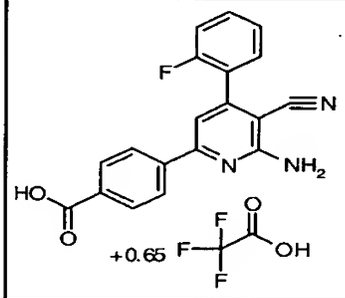
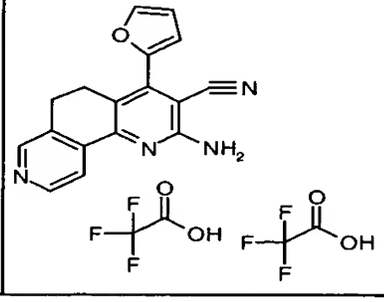
Table I: Aminocyanopyridine MK-2 Inhibitors

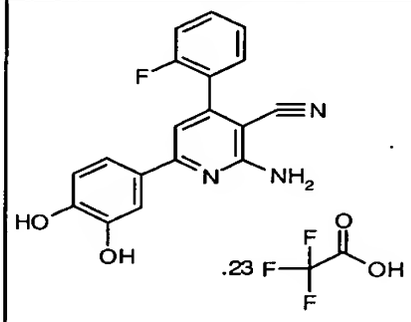
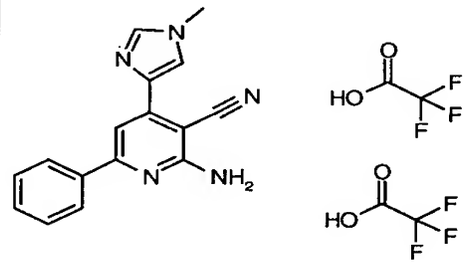
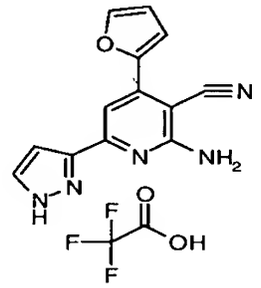
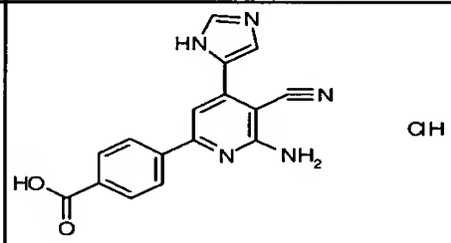
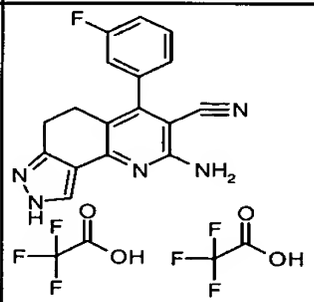
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
1		2-amino-4-(2-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	1.22
2		2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	1.36
3		2-amino-4-(2,3-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	1.95
4		8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile	1.96
5		2-amino-3-cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid trifluoroacetate	2.35

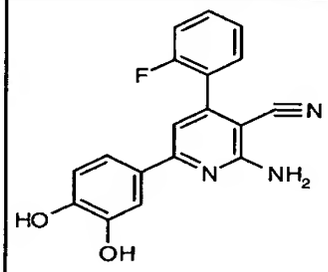
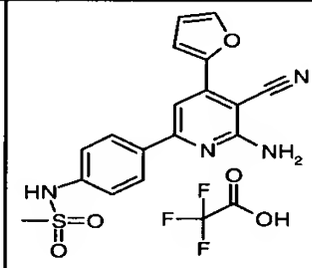
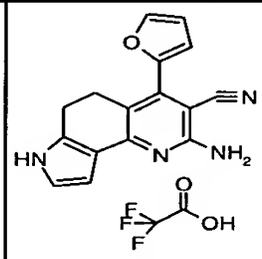
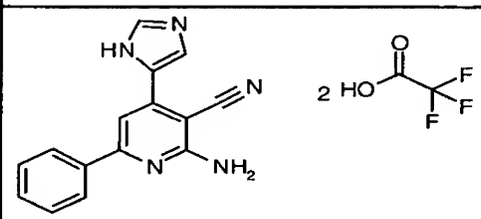
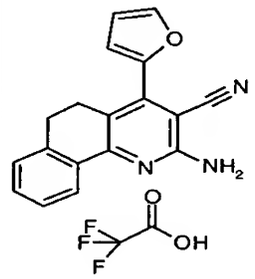
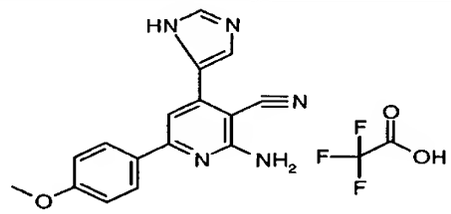
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
6		4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxamide	2.41
7		2-amino-4-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	2.73
8		2-amino-6-(2-furyl)-4-(1-methyl-1H-imidazol-4-yl)nicotinonitrile bis(trifluoroacetate)	2.88

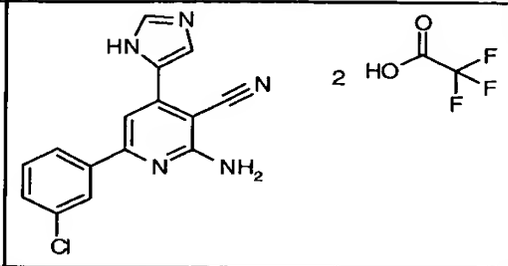
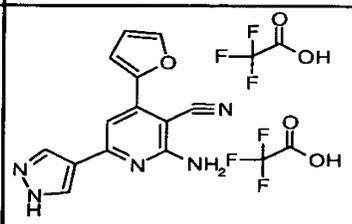
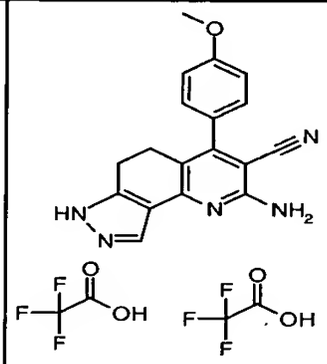
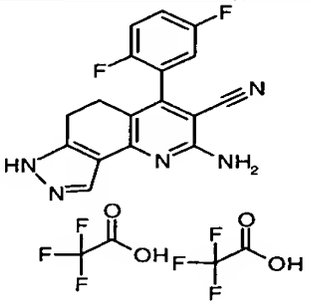
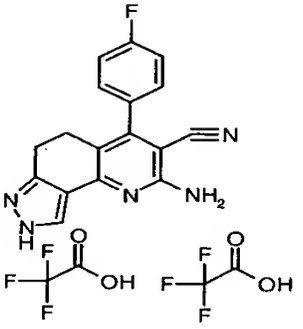
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
9		8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile trifluoroacetate	3.23
10		2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	3.48
11		2-amino-4-(2,6-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	3.59
12		2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	3.62
13		2-amino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile	4.06
14		2-amino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	4.41

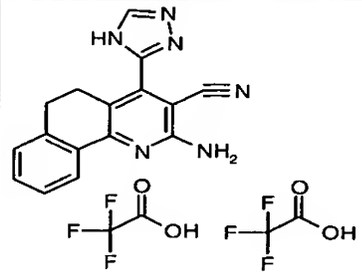
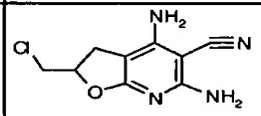
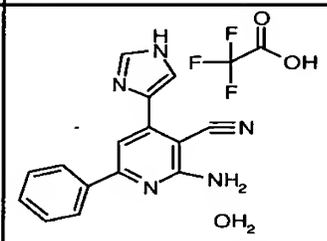
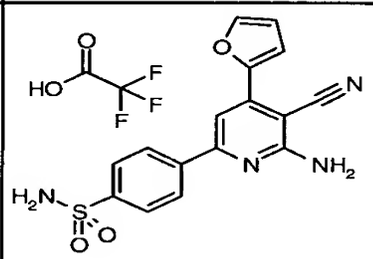
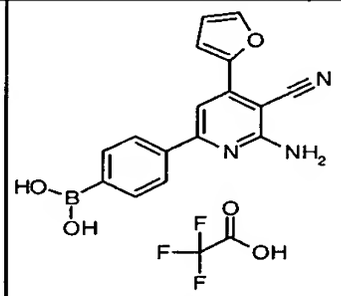
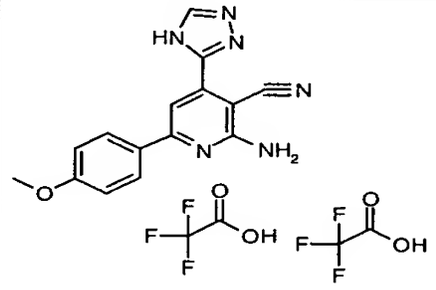
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
15		2-amino-4-(2-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	4.47
16		4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoic acid trifluoroacetate	4.63
17		2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	4.94
18		2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile	5.46
19		2-amino-3-cyano-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid bis(trifluoroacetate)	5.74
20		2-amino-6-(3-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	5.81

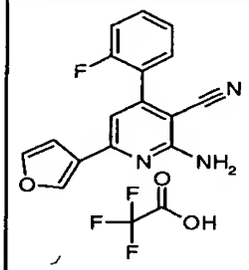
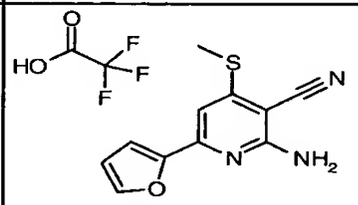
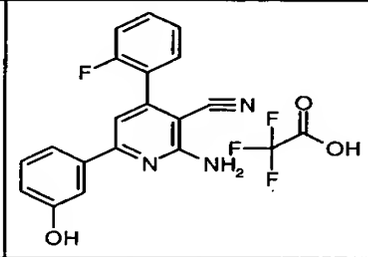
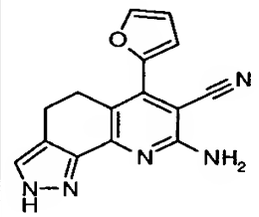
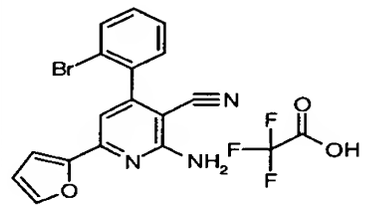
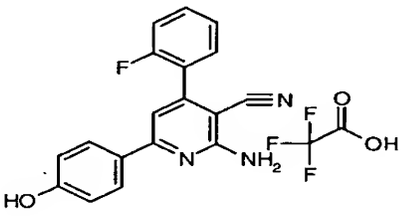
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
21		2-amino-6-(2-furyl)-4-(1H-imidazol-4-yl)nicotinonitrile trifluoroacetate hydrate	5.95
22		2-amino-4-(2,4-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	6
23		4,6-diamino-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile or 6N009	6.14
24		2-amino-4-(2-furyl)-6,8-dihydro-5H-pyrrolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	6.2
25		4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoic acid trifluoroacetate	6.4
26		2-amino-4-(2-furyl)-5,6-dihydro-1,8-phenanthroline-3-carbonitrile bis(trifluoroacetate)	6.48

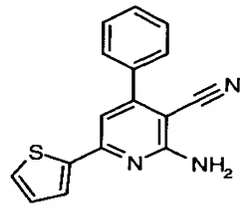
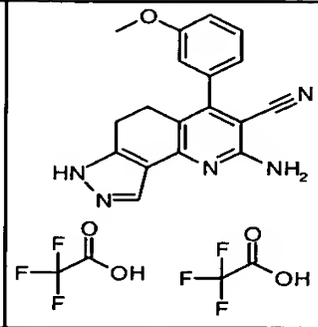
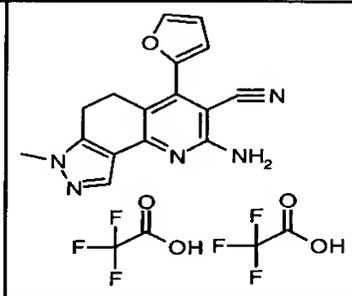
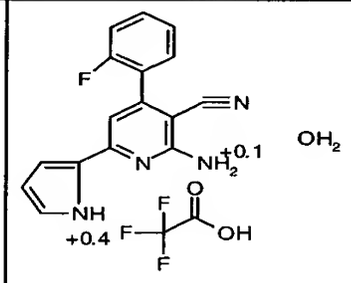
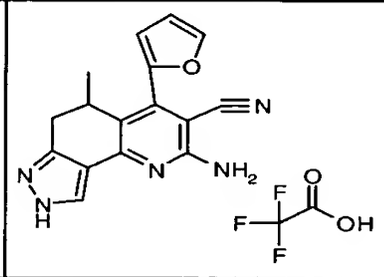
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
27		2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile trifluoroacetate	7.54
28		2-amino-4-(1-methyl-1H-imidazol-4-yl)-6-phenylnicotinonitrile bis(trifluoroacetate)	7.63
29		2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile trifluoroacetate	7.72
30		4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoic acid hydrochloride	8.37
31		2-amino-4-(3-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	8.5

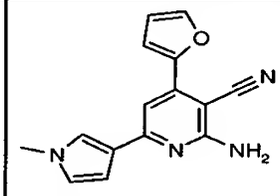
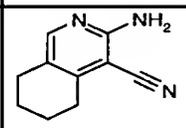
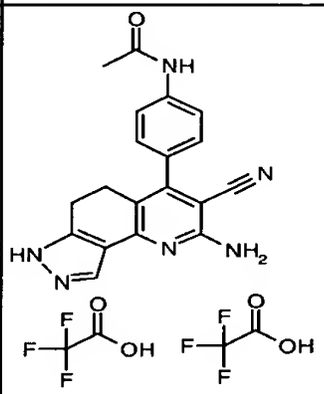
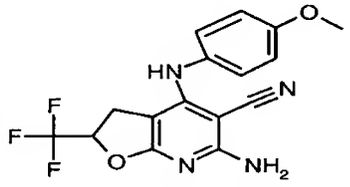
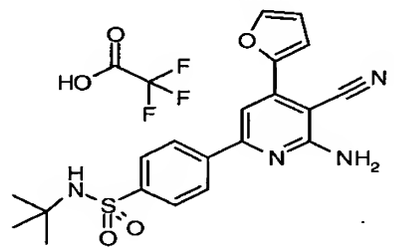
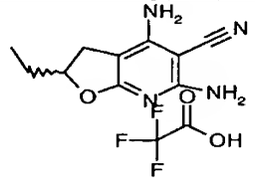
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
32		2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile	9.2
33		N-{4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenyl}methanesulfonamide trifluoroacetate	9.27
34		2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrrolo[2,3-h]quinoline-3-carbonitrile trifluoroacetate	9.4
35		2-amino-4-(1H-imidazol-5-yl)-6-phenylnicotinonitrile trifluoroacetate	9.4
36		2-amino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	9.42
37		2-amino-4-(1H-imidazol-5-yl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	9.43

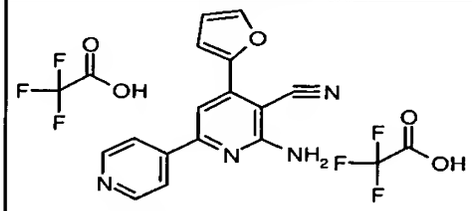
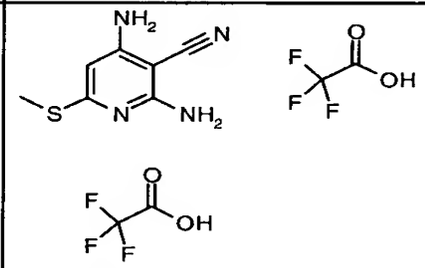
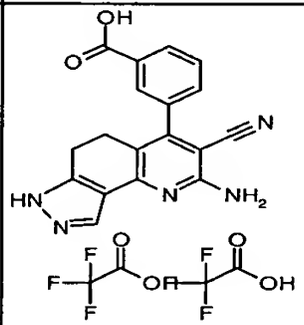
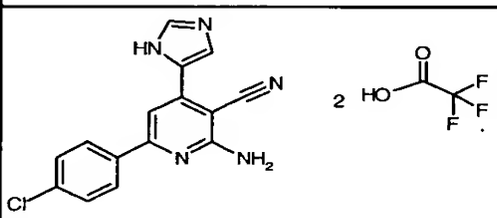
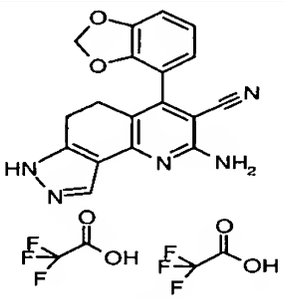
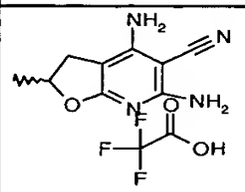
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
38		2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	10
39		2-amino-4-(2-furyl)-6-(1H-pyrazol-4-yl)nicotinonitrile bis(trifluoroacetate)	11.6
40		2-amino-4-(4-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	12
41		2-amino-4-(2,5-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	12.8
42		2-amino-4-(4-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	12.9

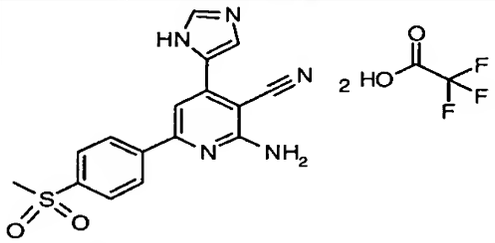
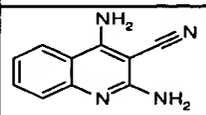
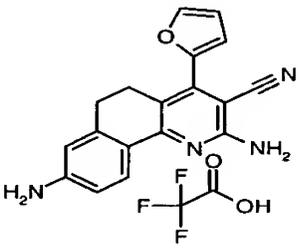
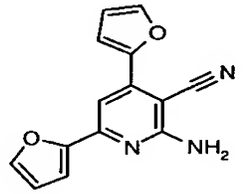
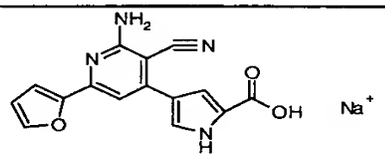
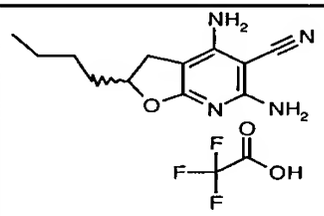
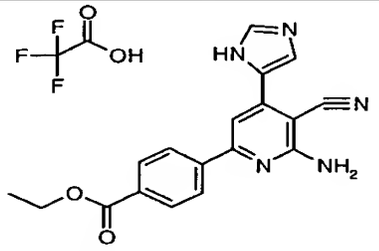
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
43		2-amino-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile bis(trifluoroacetate)	13.1
44		4,6-diamino-2-(chloromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	13.4
45		2-amino-4-(1H-imidazol-4-yl)-6-phenylnicotinonitrile trifluoroacetate hydrate	14.2
46		4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzenesulfonamide trifluoroacetate	16.1
47		4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenylboronic acid trifluoroacetate	16.7
48		2-amino-6-(4-methoxyphenyl)-4-(4H-1,2,4-triazol-3-yl)nicotinonitrile bis(trifluoroacetate)	17.3

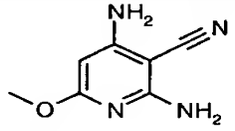
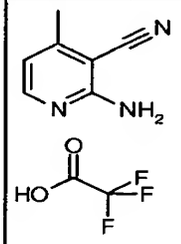
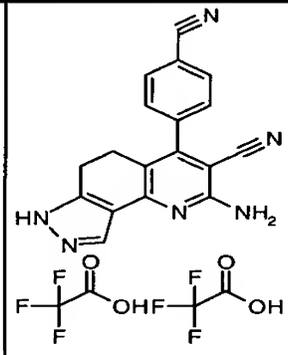
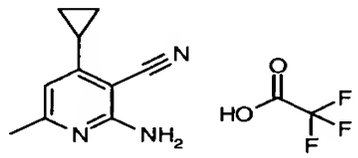
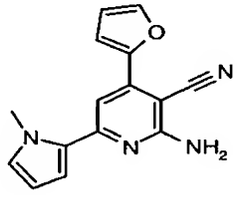
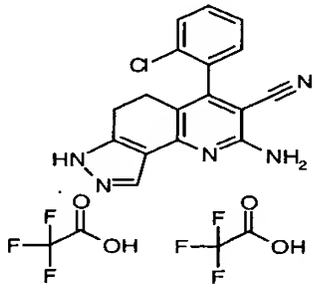
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
49		2-amino-4-(2-fluorophenyl)-6-(3-furyl)nicotinonitrile trifluoroacetate	17.9
50		2-amino-6-(2-furyl)-4-(methylthio)nicotinonitrile trifluoroacetate	22.5
51		2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	24.2
52		8-amino-6-(2-furyl)-4,5-dihydro-2H-pyrazolo[4,3-h]quinoline-7-carbonitrile	25.3
53		2-amino-4-(2-bromophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	26.1
54		2-amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	26.8

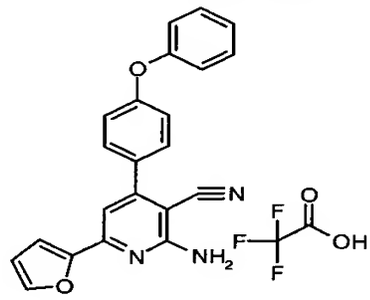
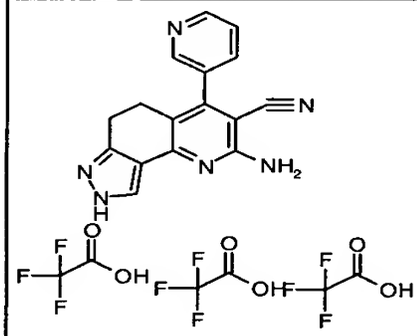
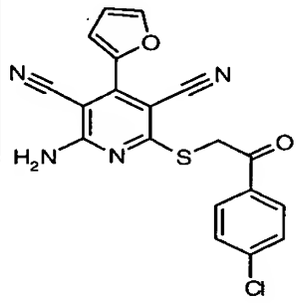
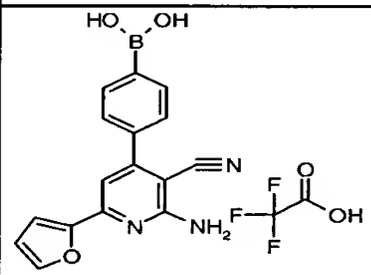
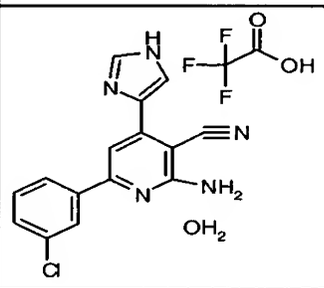
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
55		2-amino-4-phenyl-6-thien-2-ylnicotinonitrile	26.9
56		2-amino-4-(3-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	27.8
57		2-amino-4-(2-furyl)-7-methyl-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	28.3
58		2-amino-4-(2-fluorophenyl)-6-(1H-pyrrol-2-yl)nicotinonitrile trifluoroacetate hydrate	29.3
59		2-amino-4-(2-furyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	31.3

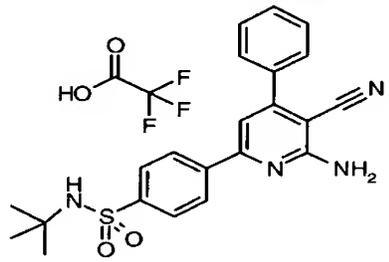
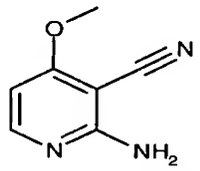
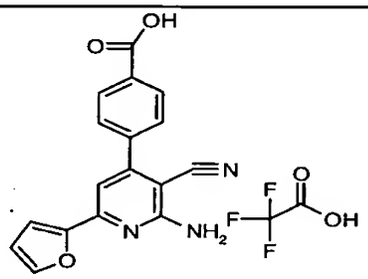
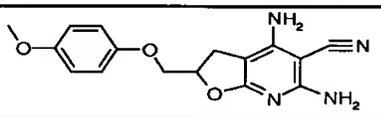
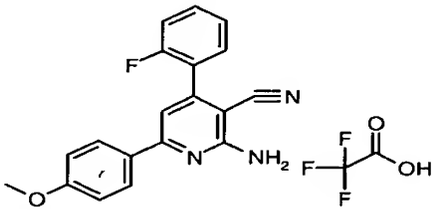
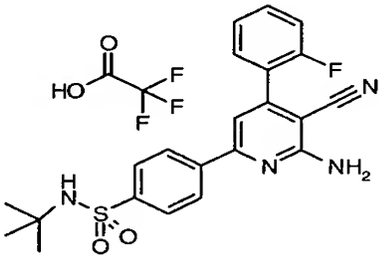
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
60		2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-3-yl)nicotinonitrile	32.1
61		3-amino-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile	33.4
62		N-[4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenyl]acetamide bis(trifluoroacetate)	35.9
63		6-amino-4-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	36.4
64		4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]-N-(tert-butyl)benzenesulfonamide trifluoroacetate	36.4
65		4,6-diamino-2-ethyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	37.9

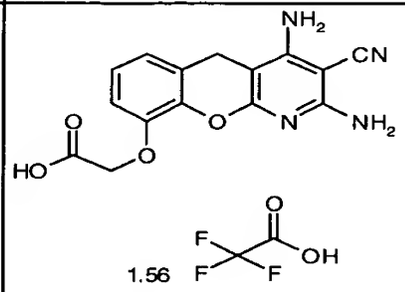
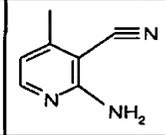
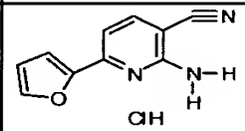
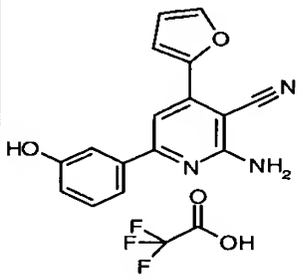
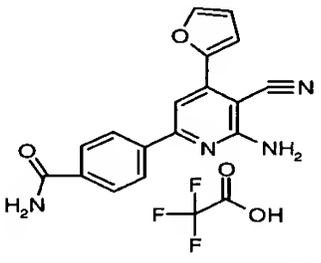
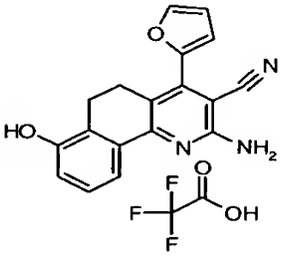
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
66		6-amino-4-(2-furyl)-2,4'-bipyridine-5-carbonitrile bis(trifluoroacetate)	39.9
67		2,4-diamino-6-(methylthio)nicotinonitrile bis(trifluoroacetate)	41.6
68		3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	41.7
69		2-amino-6-(4-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	42.9
70		2-amino-4-(1,3-benzodioxol-4-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	43.2
71		4,6-diamino-2-methyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	44.1

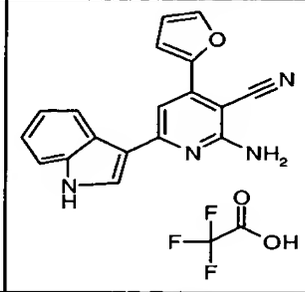
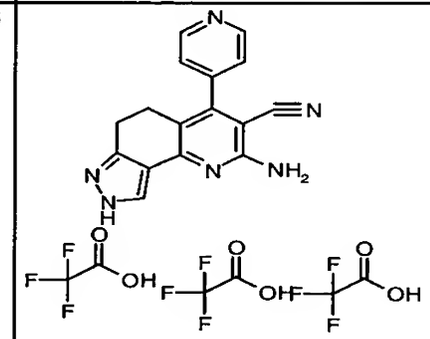
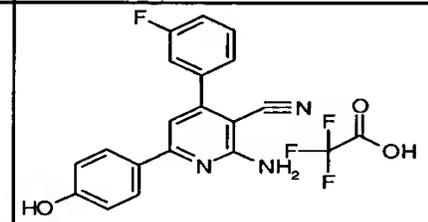
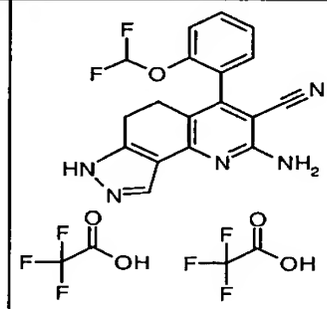
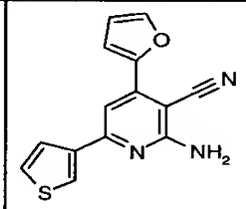
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
72		2-amino-4-(1H-imidazol-5-yl)-6-[4-(methylsulfonyl)phenyl]nicotinonitrile trifluoroacetate	45.3
73		2,4-diaminoquinoline-3-carbonitrile	45.5
74		2,8-diamino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	46.8
75		2-amino-4,6-di(2-furyl)nicotinonitrile	47.6
76		sodium 4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxylate	48.7
77		4,6-diamino-2-butyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	49.1
78		ethyl 4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoate trifluoroacetate	49.1

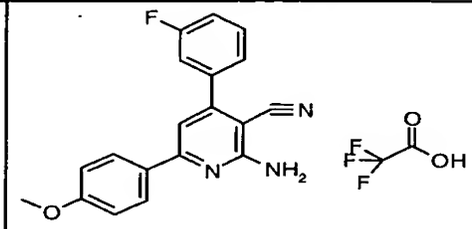
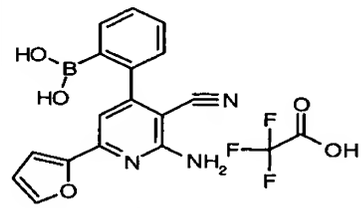
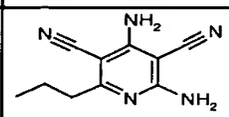
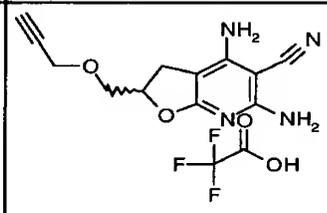
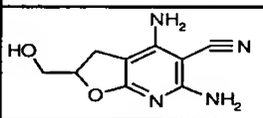
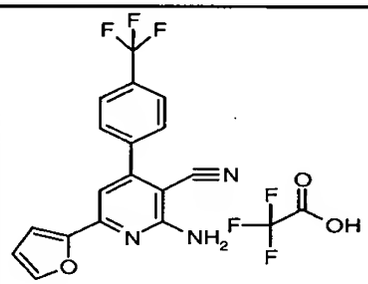
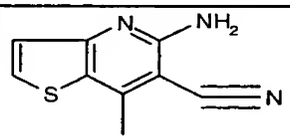
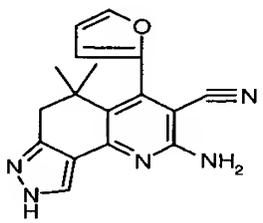
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
79		2,4-diamino-6-methoxynicotinonitrile	50.9
80		2-amino-4-methylnicotinonitrile trifluoroacetate	51.9
81		2-amino-4-(4-cyanophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	52.1
82		2-amino-4-cyclopropyl-6-methylnicotinonitrile trifluoroacetate	53.7
83		2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-2-yl)nicotinonitrile	54.4
84		2-amino-4-(2-chlorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	58.4

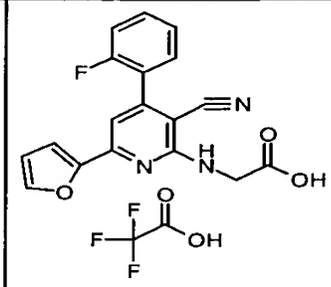
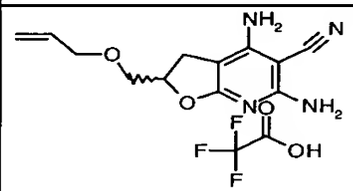
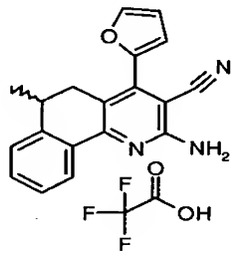
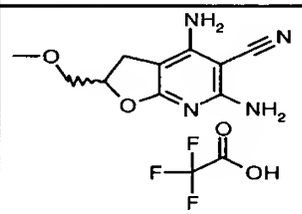
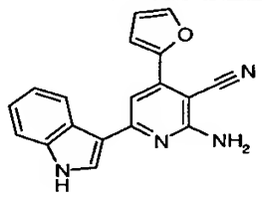
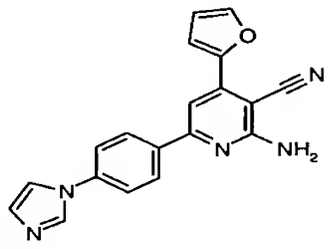
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
85		2-amino-6-(2-furyl)-4-(4-phenoxyphenyl)nicotinonitrile trifluoroacetate	59.3
86		2-amino-4-pyridin-3-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile tris(trifluoroacetate)	62.5
87		2-amino-6-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-(2-furyl)pyridine-3,5-dicarbonitrile	63.3
88		4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid trifluoroacetate	64.6
89		2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-4-yl)nicotinonitrile trifluoroacetate hydrate	64.9

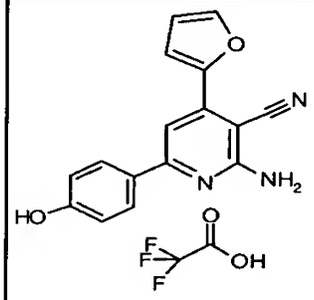
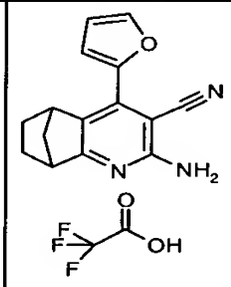
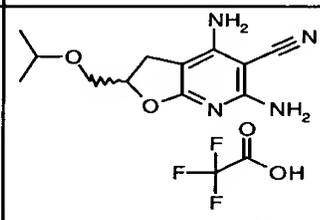
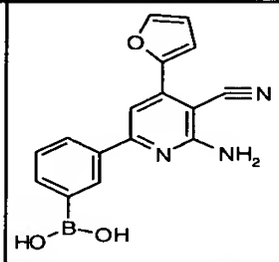
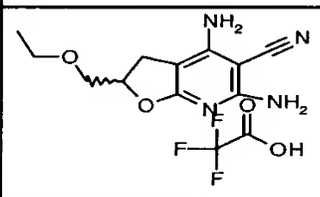
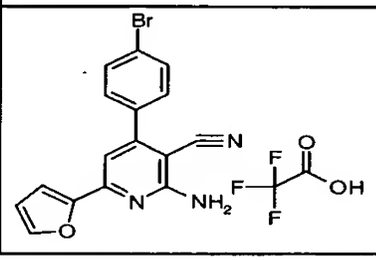
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
90		4-(6-amino-5-cyano-4-phenylpyridin-2-yl)-N-(tert-butyl)benzenesulfonamide trifluoroacetate	68
91		2-amino-4-methoxynicotinonitrile	69.6
92		4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]benzoic acid trifluoroacetate	69.8
93		4,6-diamino-2-[(4-methoxyphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	69.8
94		2-amino-4-(2-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	70.4
95		4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]-N-(tert-butyl)benzenesulfonamide trifluoroacetate	71.5

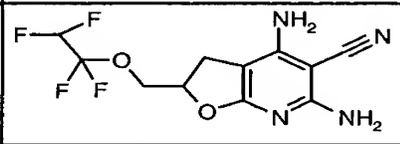
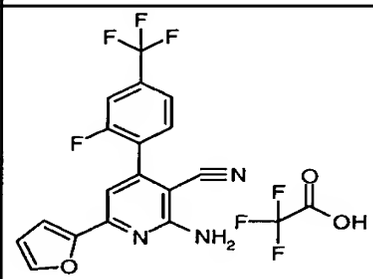
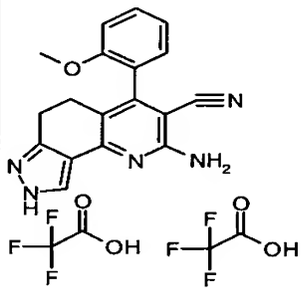
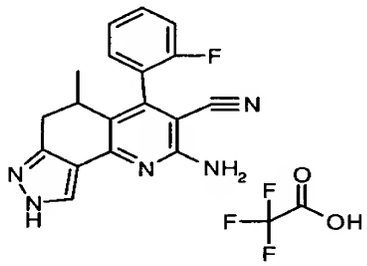
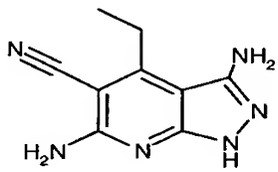
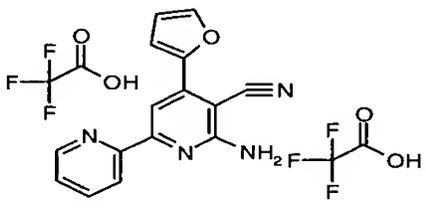
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
96		[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	72.2
97		3-Pyridinecarbonitrile, 2-Amino-4-Methyl-	77
98		2-amino-6-(2-furyl)nicotinonitrile hydrochloride	77.5
99		2-amino-4-(2-furyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	77.9
100		4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzamide trifluoroacetate	78.5
101		2-amino-4-(2-furyl)-7-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	82.6

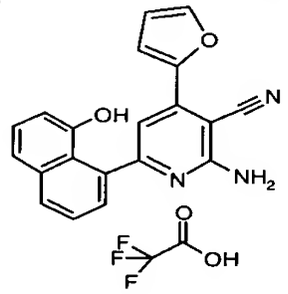
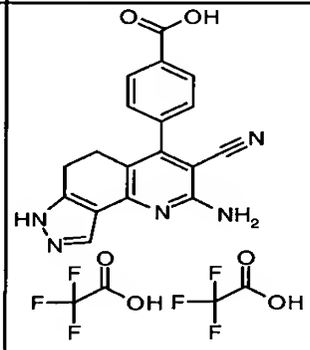
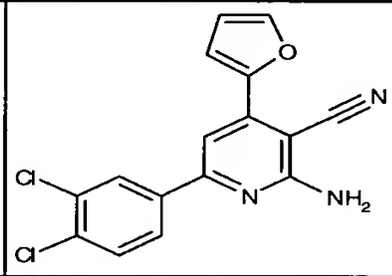
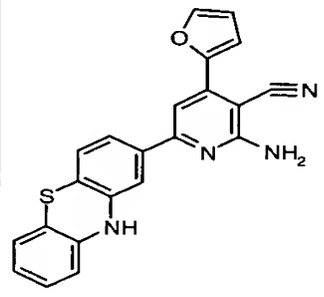
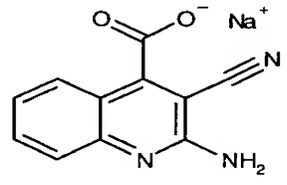
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
102		2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile trifluoroacetate	87.1
103		2-amino-4-pyridin-4-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile tris(trifluoroacetate)	94.3
104		2-amino-4-(3-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	96
105		2-amino-4-[2-(difluoromethoxy)phenyl] 6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	96.1
106		2-amino-4-(2-furyl)-6-thien-3-ylnicotinonitrile	97.3

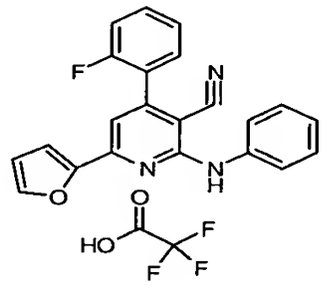
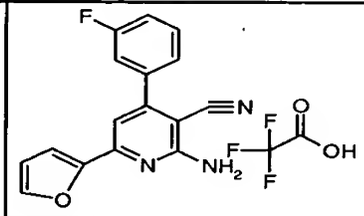
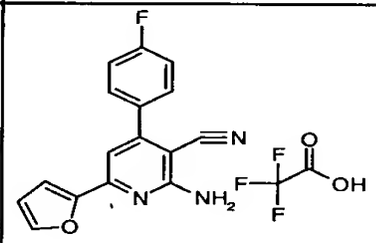
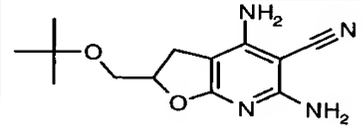
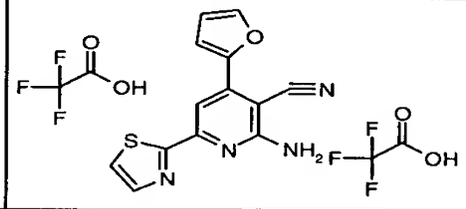
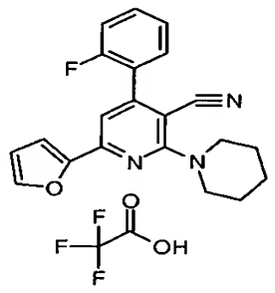
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
107		2-amino-4-(3-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	97.3
108		2-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid trifluoroacetate	99.6
109		2,4-diamino-6-propylpyridine-3,5-dicarbonitrile	99.8
110		4,6-diamino-2-[(prop-2-ynyloxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	105
111		4,6-diamino-2-(hydroxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	106
112		2-amino-6-(2-furyl)-4-[4-(trifluoromethyl)phenyl]nicotinonitrile trifluoroacetate	107
113		5-amino-7-methylthieno[3,2-b]pyridine-6-carbonitrile or GK02302	109
114		2-amino-4-(2-furyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile	109

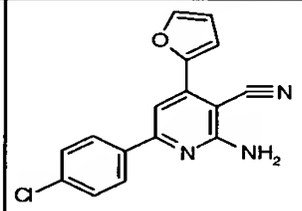
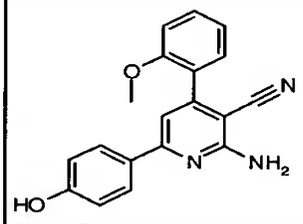
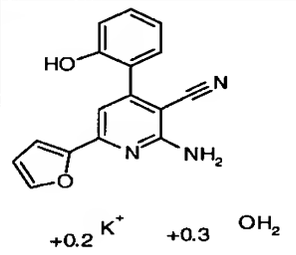
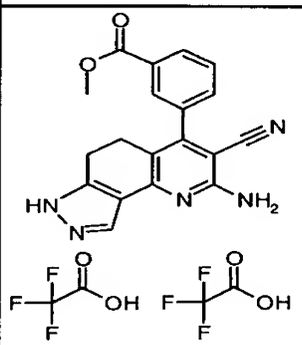
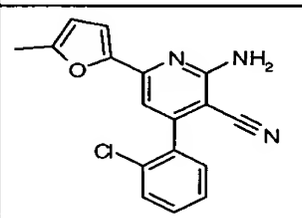
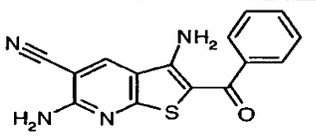
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
115		N-[3-cyano-4-(2-fluorophenyl)-6-(2-furyl)pyridin-2-yl]glycine trifluoroacetate	114
116		2-[(allyloxy)methyl]-4,6-diamino-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	118
117		2-amino-4-(2-furyl)-6-methyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	119
118		4,6-diamino-2-(methoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	119
119		2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile	120
120		2-amino-4-(2-furyl)-6-[4-(1H-imidazol-1-yl)phenyl]nicotinonitrile	121

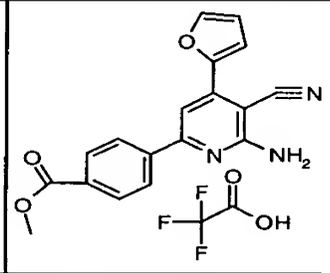
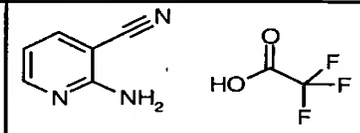
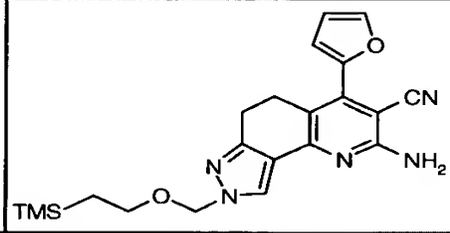
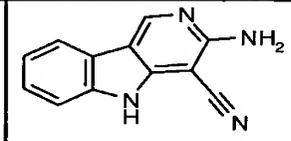
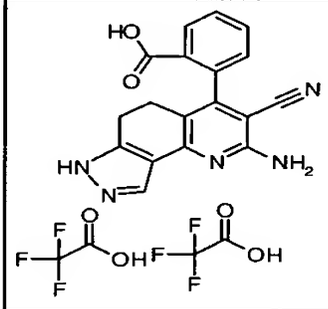
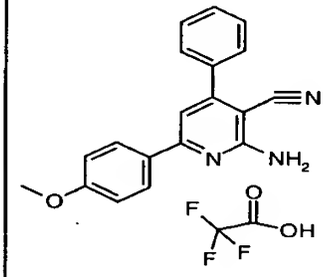
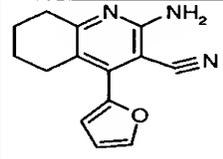
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
121		2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	122
122		2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-3-carbonitrile trifluoroacetate	122
123		4,6-diamino-2-(isopropoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	125
124		3-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenylboronic acid	126
125		4,6-diamino-2-(ethoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	127
126		2-amino-4-(4-bromophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	130

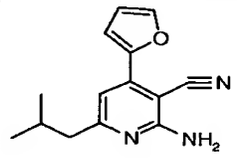
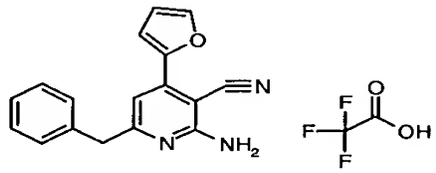
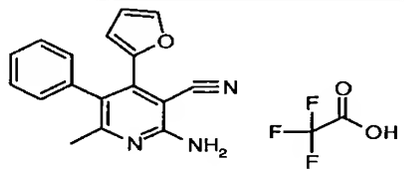
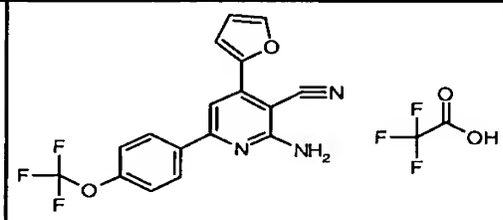
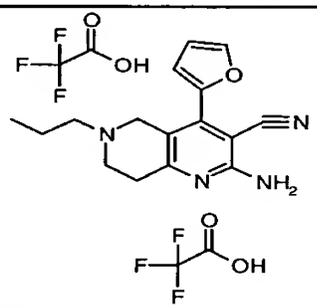
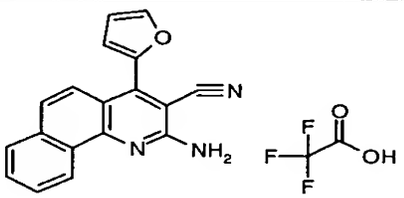
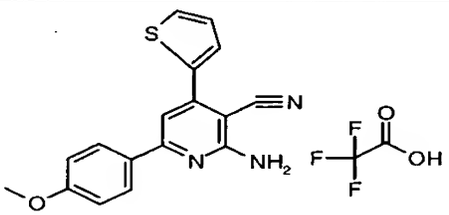
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
127		4,6-diamino-2-[(1,1,2,2-tetrafluoroethoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	131
128		2-amino-4-[2-fluoro-4-(trifluoromethyl)phenyl]-6-(2-furyl)nicotinonitrile trifluoroacetate	133
129		2-amino-4-(2-methoxyphenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	136
130		2-amino-4-(2-fluorophenyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	142
131		3,6-diamino-4-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile	146
132		6-amino-4-(2-furyl)-2,2'-bipyridine-5-carbonitrile bis(trifluoroacetate)	149

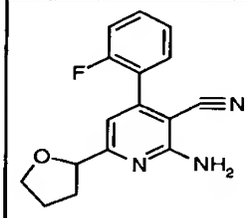
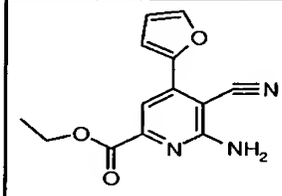
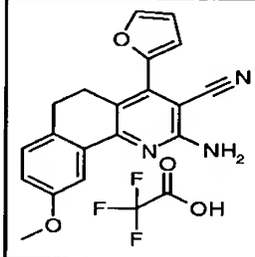
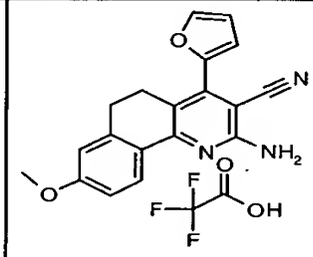
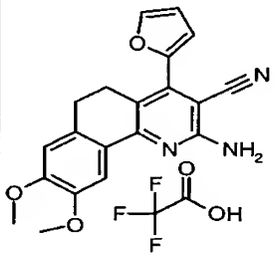
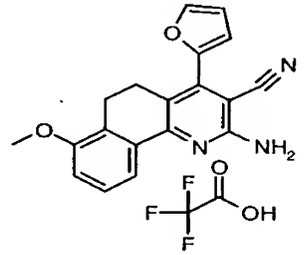
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
133		2-amino-4-(2-furyl)-6-(8-hydroxy-1-naphthyl)nicotinonitrile trifluoroacetate	153
134		4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	155
135		2-amino-6-(3,4-dichlorophenyl)-4-(2-furyl)nicotinonitrile	156
136		2-amino-4-(2-furyl)-6-(10H-phenothiazin-2-yl)nicotinonitrile	158
137		sodium 2-amino-3-cyano-4-quinolinecarboxylate	161

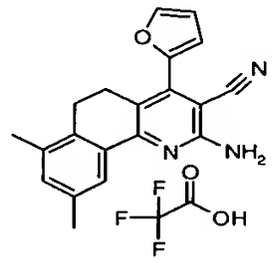
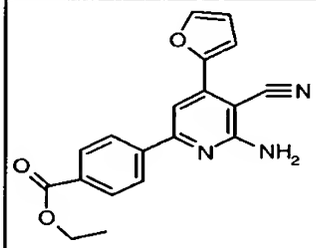
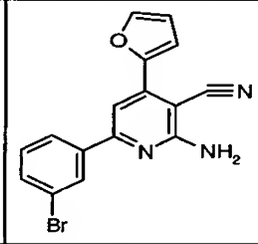
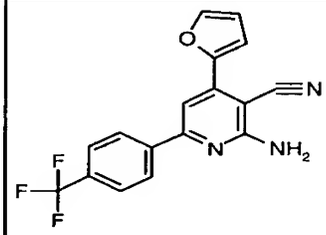
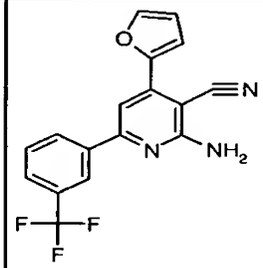
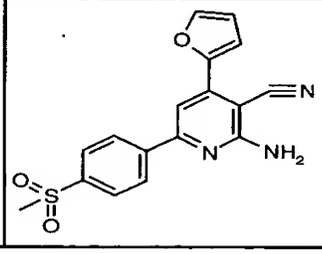
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
138		2-anilino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile	162
139		2-amino-4-(3-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	164
140		2-amino-4-(4-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	165
141		4,6-diamino-2-(tert-butoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	167
142		2-amino-4-(2-furyl)-6-(1,3-thiazol-2-yl)nicotinonitrile bis(trifluoroacetate)	167
143		4-(2-fluorophenyl)-6-(2-furyl)-2-piperidin-1-ylnicotinonitrile trifluoroacetate	176

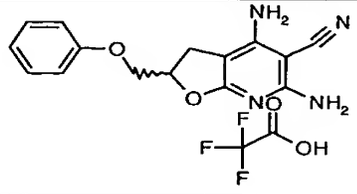
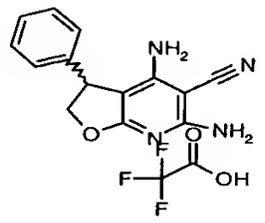
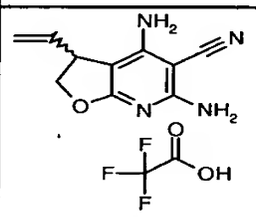
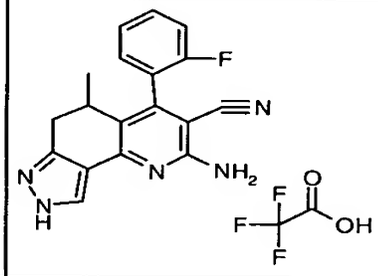
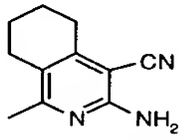
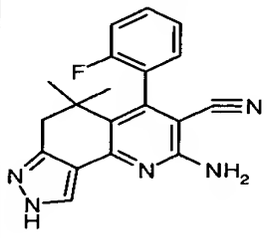
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
144		2-amino-6-(4-chlorophenyl)-4-(2-furyl)nicotinonitrile	182
145		2-amino-6-(4-hydroxyphenyl)-4-(2-methoxyphenyl)nicotinonitrile	183
146		2-amino-6-(2-furyl)-4-(2-hydroxyphenyl)nicotinonitrile	185
147		methyl 3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	191
148		2-amino-4-(2-chlorophenyl)-6-(5-methyl-2-furyl)nicotinonitrile	192
149		3,6-diamino-2-benzoylthieno[2,3-b]pyridine-5-carbonitrile	199

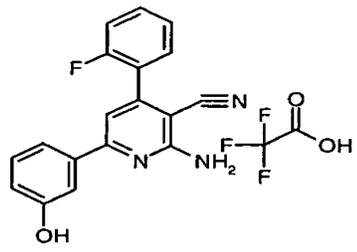
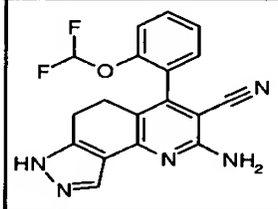
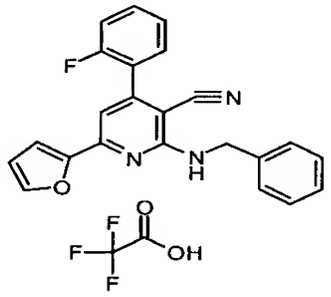
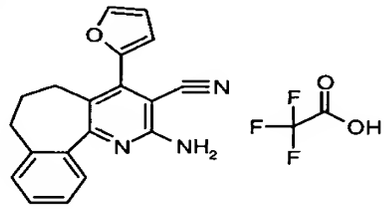
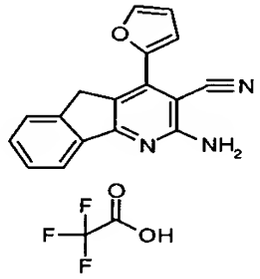
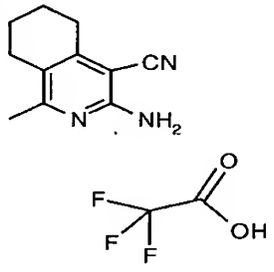
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
150		methyl 4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoate trifluoroacetate	199
151		2-aminonicotinonitrile trifluoroacetate	200
152		2-amino-4-(2-furyl)-8-{[2-(trimethylsilyl)ethoxy]methyl}-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile	200
153		3-amino-5H-pyrido[4,3-b]indole-4-carbonitrile	200
154		2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	200
155		2-amino-6-(4-methoxyphenyl)-4-phenylnicotinonitrile trifluoroacetate	200
156		2-amino-4-(2-furyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile	200

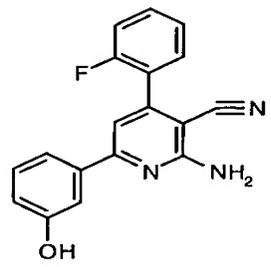
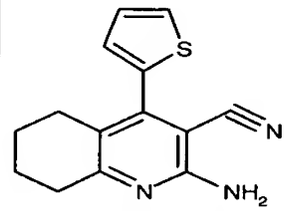
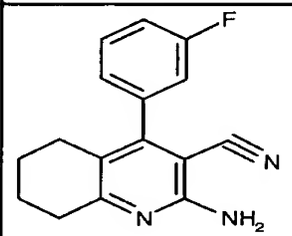
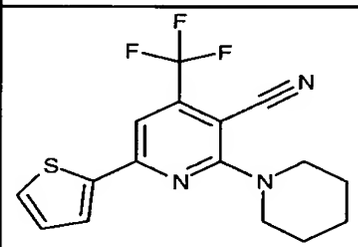
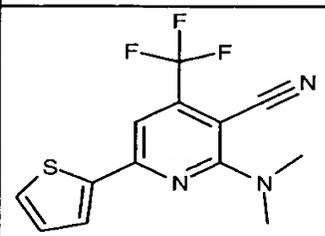
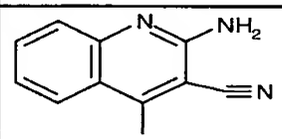
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
157		2-amino-4-(2-furyl)-6-isobutylnicotinonitrile	200
158		2-amino-6-benzyl-4-(2-furyl)nicotinonitrile trifluoroacetate	200
159		2-amino-4-(2-furyl)-6-methyl-5-phenylnicotinonitrile trifluoroacetate	200
160		2-amino-4-(2-furyl)-6-[4-(trifluoromethoxy)phenyl]nicotinonitrile trifluoroacetate	200
161		2-amino-4-(2-furyl)-6-propyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile bis(trifluoroacetate)	200
162		2-amino-4-(2-furyl)benzo[h]quinoline-3-carbonitrile trifluoroacetate	200
163		2-amino-6-(4-methoxyphenyl)-4-thien-2-ylnicotinonitrile trifluoroacetate	200

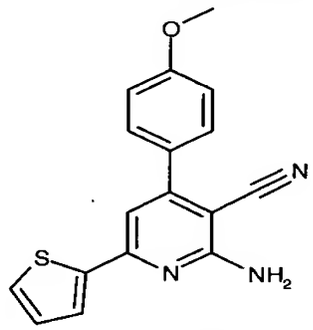
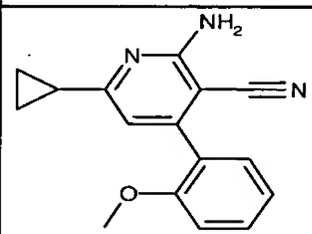
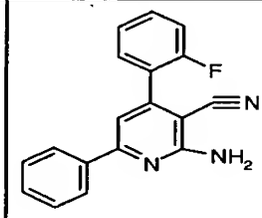
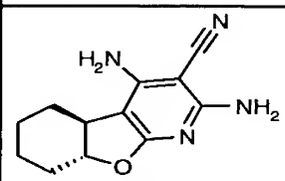
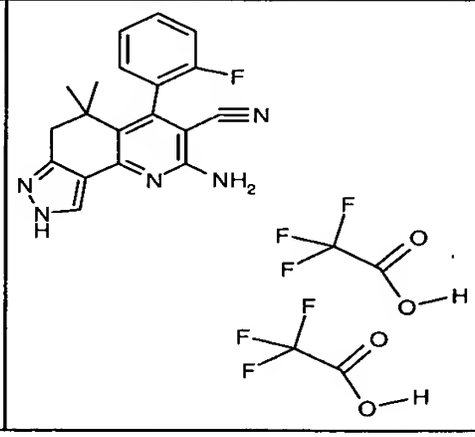
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
164		2-amino-4-(2-fluorophenyl)-6-tetrahydrofuran-2-ylnicotinonitrile	200
165		ethyl 6-amino-5-cyano-4-(2-furyl)pyridine-2-carboxylate	200
166		2-amino-4-(2-furyl)-9-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200
167		2-amino-4-(2-furyl)-8-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200
168		2-amino-4-(2-furyl)-8,9-dimethoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200
169		2-amino-4-(2-furyl)-7-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200

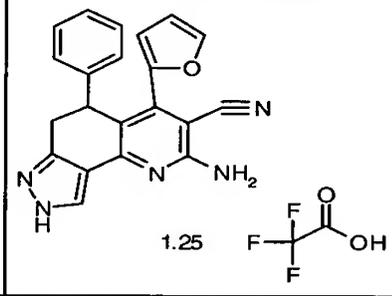
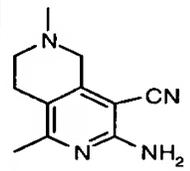
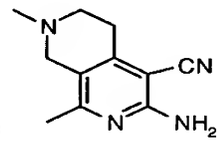
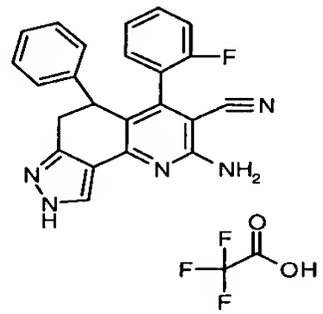
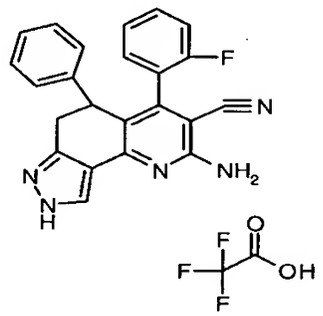
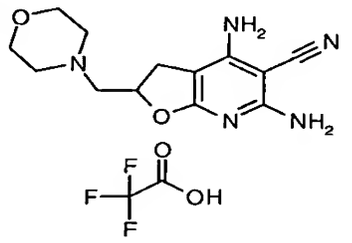
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
170		2-amino-4-(2-furyl)-7,9-dimethyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200
171		ethyl 4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoate	200
172		2-amino-6-(3-bromophenyl)-4-(2-furyl)nicotinonitrile	200
173		2-amino-4-(2-furyl)-6-[4-(trifluoromethyl)phenyl]nicotinonitrile	200
174		2-amino-4-(2-furyl)-6-[3-(trifluoromethyl)phenyl]nicotinonitrile	200
175		2-amino-4-(2-furyl)-6-[4-(methylsulfonyl)phenyl]nicotinonitrile	200

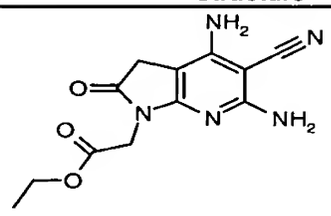
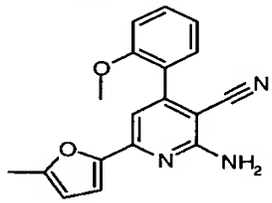
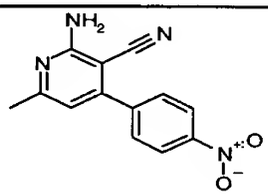
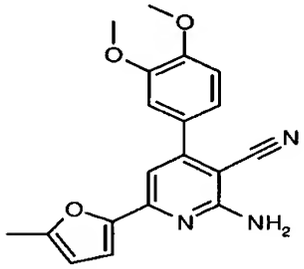
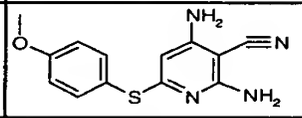
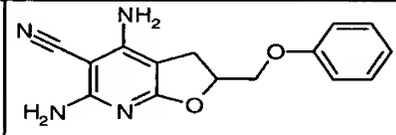
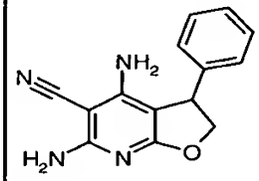
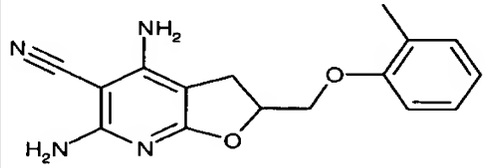
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
176		4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	200
177		4,6-diamino-3-phenyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	200
178		4,6-diamino-3-vinyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	200
179		2-amino-4-(2-fluorophenyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	200
180		3-amino-1-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile	200
181		2-amino-4-(2-fluorophenyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile	200

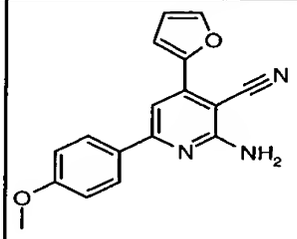
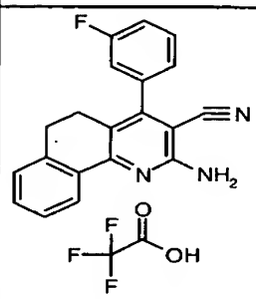
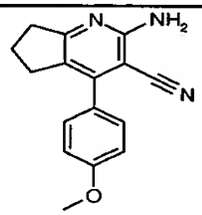
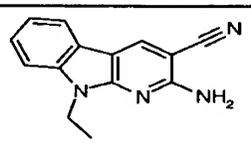
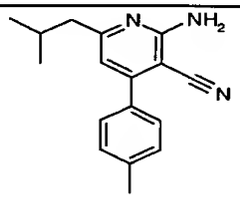
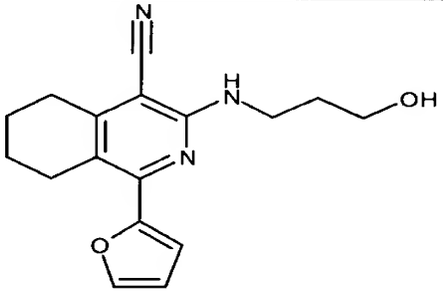
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
182		2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	200
183		2-amino-4-[2-(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile	200
184		2-(benzylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	200
185		2-amino-4-(2-furyl)-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile trifluoroacetate	200
186		2-amino-4-(2-furyl)-5H-indeno[1,2-b]pyridine-3-carbonitrile trifluoroacetate	200
187		3-amino-1-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile trifluoroacetate	200

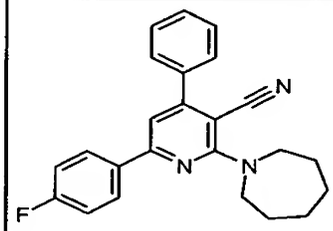
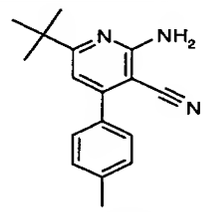
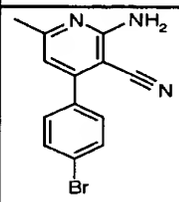
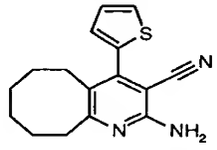
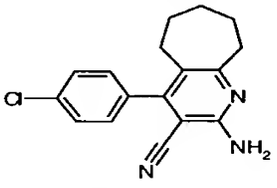
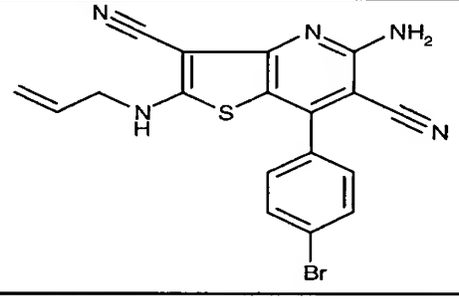
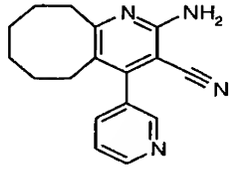
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
188		2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile	200
189		2-amino-4-(2-thienyl)-5,6,7,8-tetrahydro-3-quinolinecarbonitrile	200
190		2-amino-4-(3-fluorophenyl)-5,6,7,8-tetrahydro-3-quinolinecarbonitrile	200
191		2-(1-piperidinyl)-6-(2-thienyl)-4-(trifluoromethyl)nicotinonitrile	200
192		2-(dimethylamino)-6-(2-thienyl)-4-(trifluoromethyl)nicotinonitrile	200
193		3-Quinolinecarbonitrile, 2-amino-4-methyl- or 2-amino-4-methyl-3-quinolinecarbonitrile	200

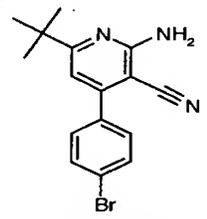
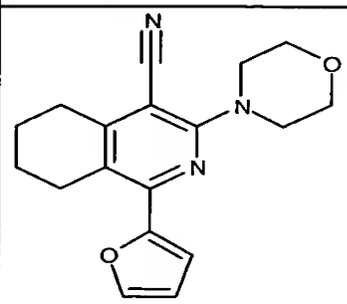
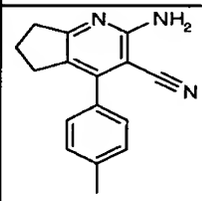
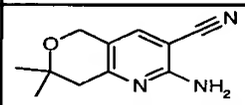
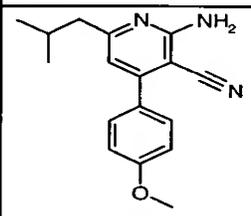
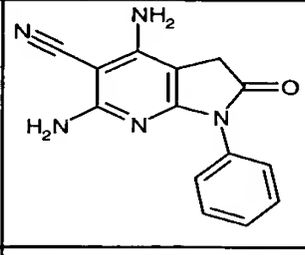
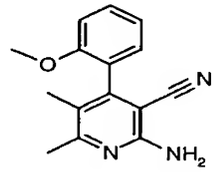
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
194		2-amino-4-(4-methoxyphenyl)-6-(2-thienyl)nicotinonitrile	200
195		2-amino-6-cyclopropyl-4-(2-methoxyphenyl)nicotinonitrile	200
196		2-amino-4-(2-fluorophenyl)-6-phenylnicotinonitrile	200
197		(4bS,8aR)-2,4-diamino-4b,5,6,7,8,8a-hexahydro[1]benzofuro[2,3-b]pyridine-3-carbonitrile	200
198		2-amino-4-(2-fluorophenyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200

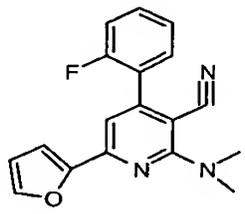
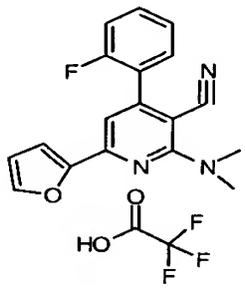
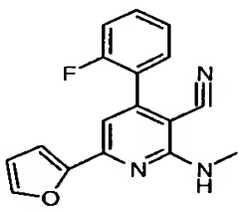
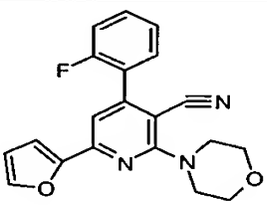
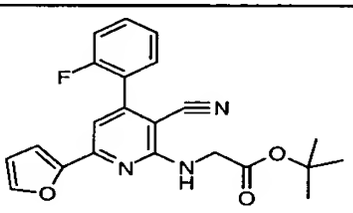
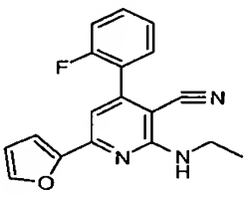
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
199		2-amino-4-(2-furyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	200
200		3-amino-1,6-dimethyl-5,6,7,8-tetrahydro-2,6-naphthyridine-4-carbonitrile	200
201		3-amino-1,7-dimethyl-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile	200
202		2-amino-4-(2-fluorophenyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	200
203		2-amino-4-(2-fluorophenyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate	200
204		4,6-diamino-2-(morpholin-4-ylmethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	200

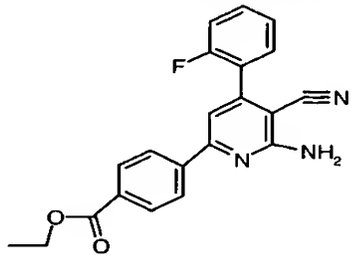
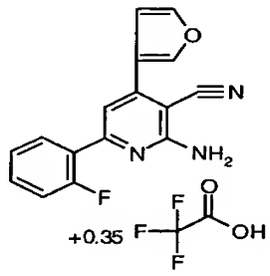
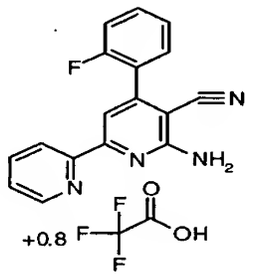
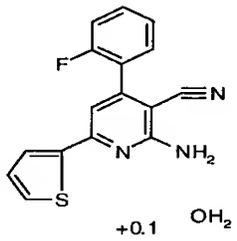
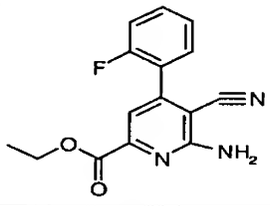
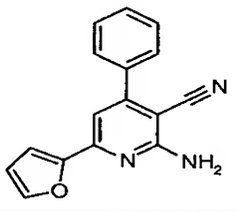
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
205		ethyl (4,6-diamino-5-cyano-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate	200
206		2-amino-4-(2-methoxyphenyl)-6-(5-methyl-2-furyl)nicotinonitrile	200
207		2-amino-6-methyl-4-(4-nitrophenyl)nicotinonitrile	200
208		2-amino-4-(3,4-dimethoxyphenyl)-6-(5-methyl-2-furyl)nicotinonitrile	200
209		2,4-diamino-6-[(4-methoxyphenyl)thio]nicotinonitrile	200
210		4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	200
211		4,6-diamino-3-phenyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	200
212		4,6-diamino-2-[(2-methylphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	200

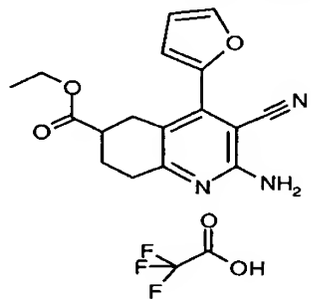
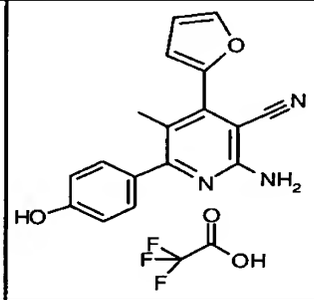
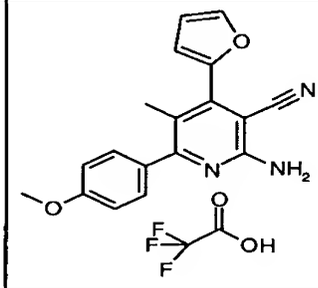
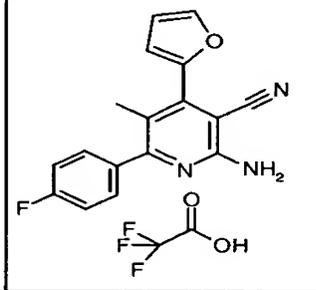
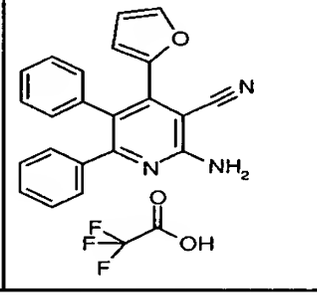
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
213		2-amino-4-(2-furyl)-6-(4-methoxyphenyl)nicotinonitrile	200
214		2-amino-4-(3-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	200
215		2-amino-4-(4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile	200
216		2-amino-9-ethyl-9H-pyrido[2,3-b]indole-3-carbonitrile	200
217		2-amino-6-isobutyl-4-(4-methylphenyl)nicotinonitrile	200
218		1-(2-furyl)-3-[(3-hydroxypropyl)amino]-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile	200

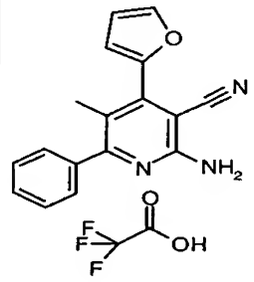
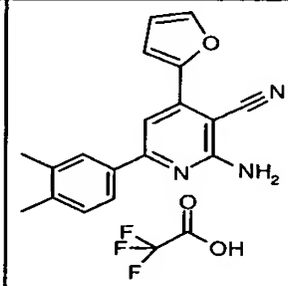
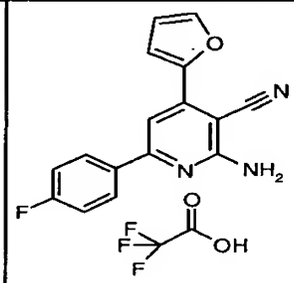
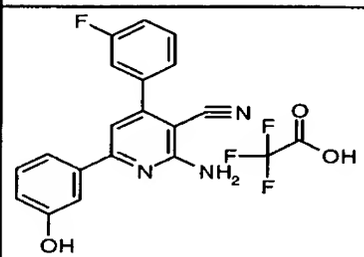
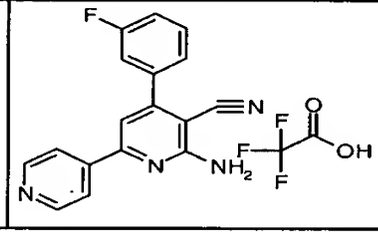
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
219		2-azepan-1-yl-6-(4-fluorophenyl)-4-phenylnicotinonitrile	200
220		2-amino-6-tert-butyl-4-(4-methylphenyl)nicotinonitrile	200
221		2-amino-4-(4-bromophenyl)-6-methylnicotinonitrile	200
222		2-amino-4-thien-2-yl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile	200
223		2-amino-4-(4-chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carbonitrile	200
224		2-(allylamino)-5-amino-7-(4-bromophenyl)thieno[3,2-b]pyridine-3,6-dicarbonitrile	200
225		2-amino-4-pyridin-3-yl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile	200

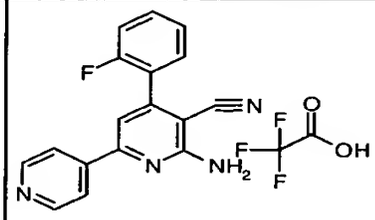
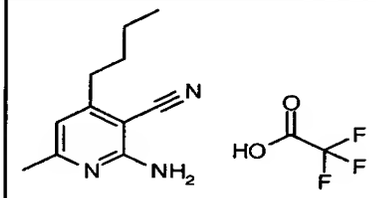
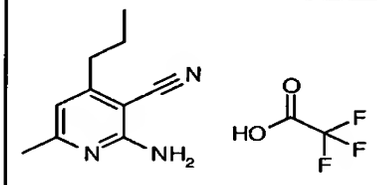
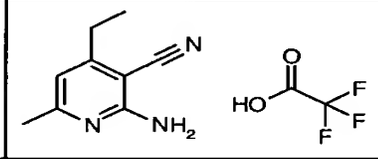
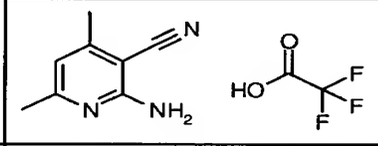
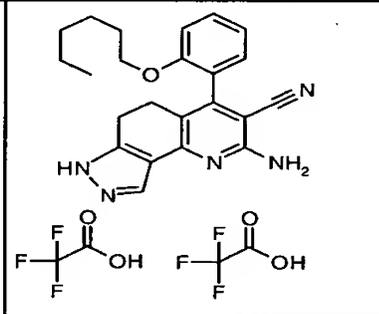
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
226		2-amino-4-(4-bromophenyl)-6-tert-butylnicotinonitrile	200
227		1-(2-furyl)-3-morpholin-4-yl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile	200
228		2-amino-4-(4-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile	200
229		2-amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile	200
230		2-amino-6-isobutyl-4-(4-methoxyphenyl)nicotinonitrile	200
231		4,6-diamino-2-oxo-1-phenyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile	200
232		2-amino-4-(2-methoxyphenyl)-5,6-dimethylnicotinonitrile	200

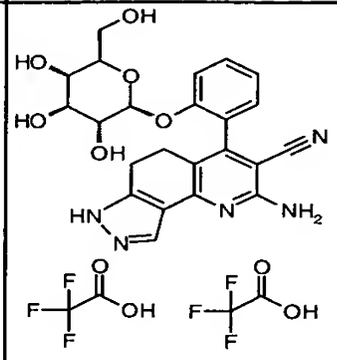
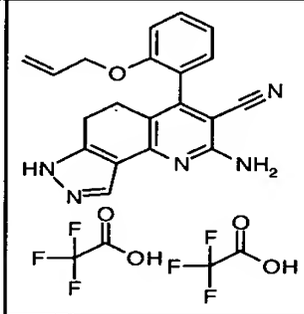
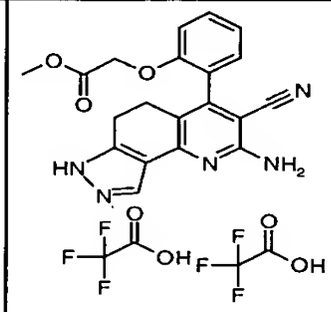
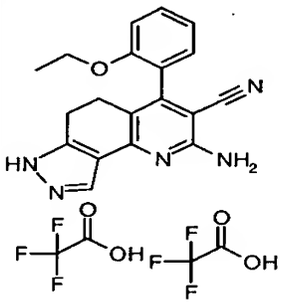
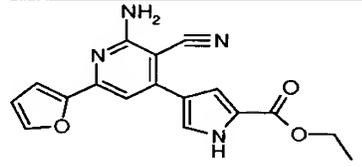
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
233		2-(dimethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile	200
234		2-(dimethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile	200
235		4-(2-fluorophenyl)-6-(2-furyl)-2-(methylamino)nicotinonitrile	200
236		4-(2-fluorophenyl)-6-(2-furyl)-2-morpholin-4-ylnicotinonitrile	200
237		tert-butyl N-[3-cyano-4-(2-fluorophenyl)-6-(2-furyl)pyridin-2-yl]glycinate	200
238		2-(ethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile	200

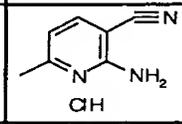
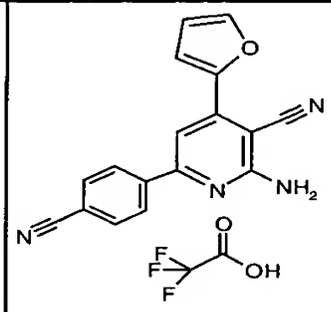
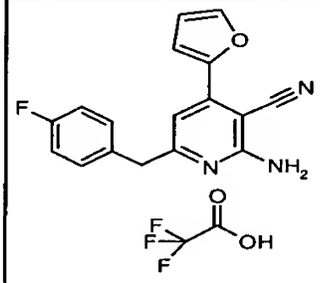
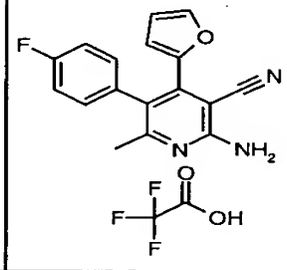
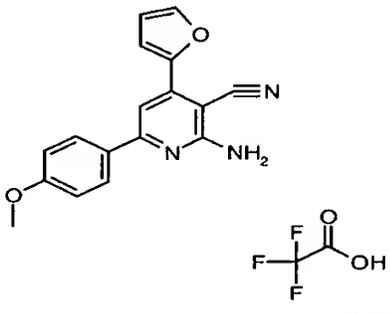
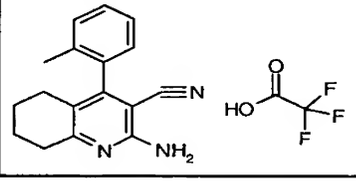
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
239		ethyl 4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoate	200
240		2-amino-6-(2-fluorophenyl)-4-(3-furyl)nicotinonitrile trifluoroacetate	200
241		6-amino-4-(2-fluorophenyl)-2,2'-bipyridine-5-carbonitrile trifluoroacetate	200
242		2-amino-4-(2-fluorophenyl)-6-thien-2-ylnicotinonitrile hydrate	200
243		ethyl 6-amino-5-cyano-4-(2-fluorophenyl)pyridine-2-carboxylate	200
244		2-amino-6-(2-furyl)-4-phenylnicotinonitrile	200

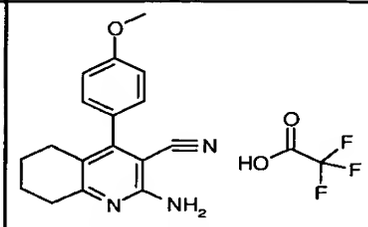
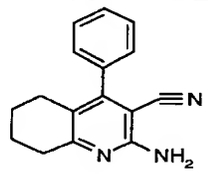
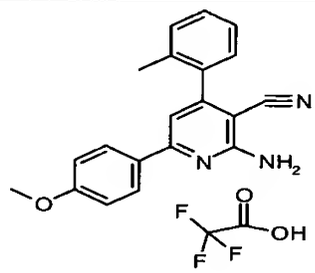
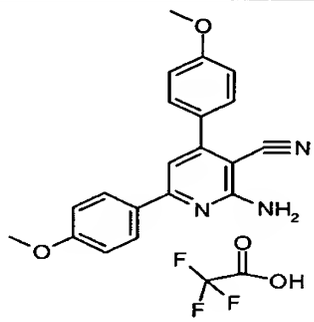
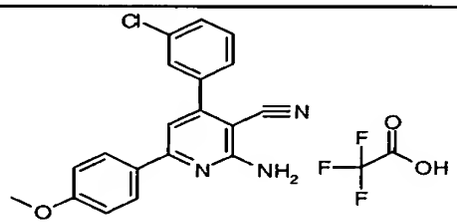
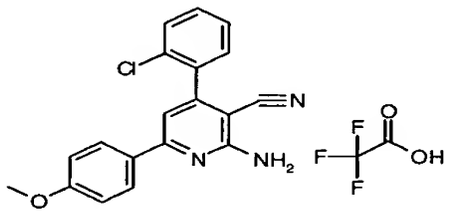
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
245		ethyl 2-amino-3-cyano-4-(2-furyl)-5,6,7,8-tetrahydroquinoline-6-carboxylate trifluoroacetate	200
246		2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)-5-methylnicotinonitrile trifluoroacetate	200
247		2-amino-4-(2-furyl)-6-(4-methoxyphenyl)-5-methylnicotinonitrile trifluoroacetate	200
248		2-amino-6-(4-fluorophenyl)-4-(2-furyl)-5-methylnicotinonitrile trifluoroacetate	200
249		2-amino-4-(2-furyl)-5,6-diphenylnicotinonitrile trifluoroacetate	200

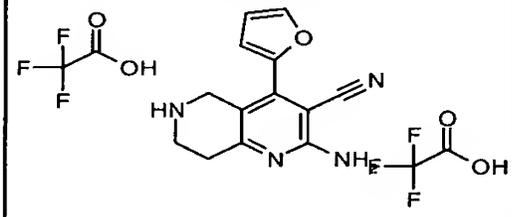
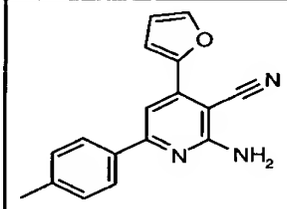
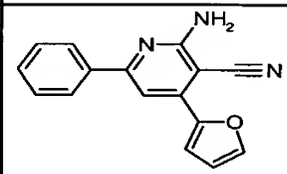
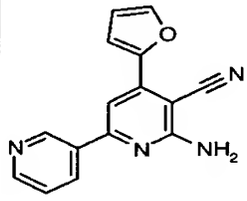
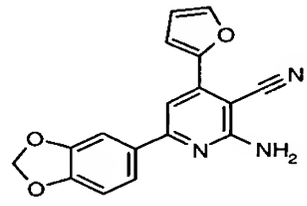
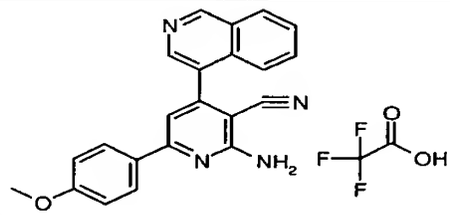
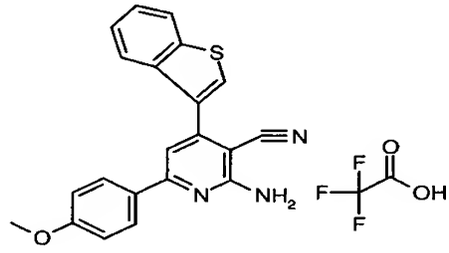
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
250		2-amino-4-(2-furyl)-5-methyl-6-phenylnicotinonitrile trifluoroacetate	200
251		2-amino-6-(3,4-dimethylphenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	200
252		2-amino-6-(4-fluorophenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	200
253		2-amino-4-(3-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	200
254		6-amino-4-(3-fluorophenyl)-2,4'-bipyridine-5-carbonitrile trifluoroacetate	200

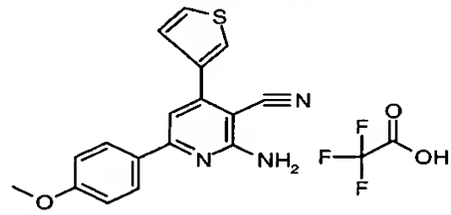
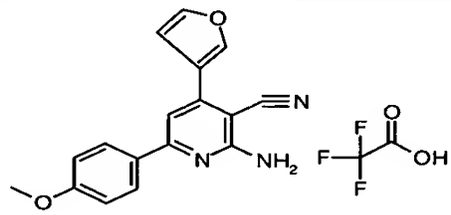
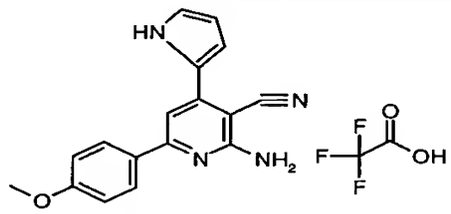
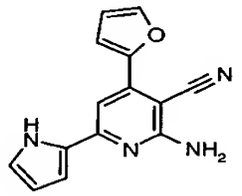
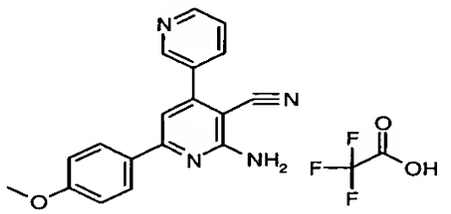
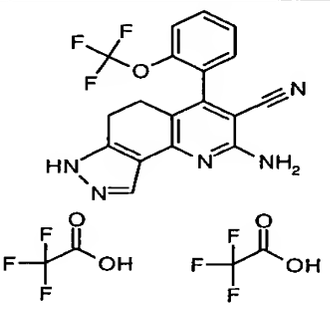
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
255		6-amino-4-(2-fluorophenyl)-2,4'-bipyridine-5-carbonitrile trifluoroacetate	200
256		2-amino-4-butyl-6-methylnicotinonitrile trifluoroacetate	200
257		2-amino-6-methyl-4-propylnicotinonitrile trifluoroacetate	200
258		2-amino-4-ethyl-6-methylnicotinonitrile trifluoroacetate	200
259		2-amino-4,6-dimethylnicotinonitrile trifluoroacetate	200
260		2-amino-4-[2-(hexyloxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200

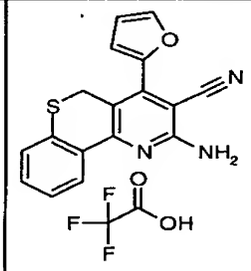
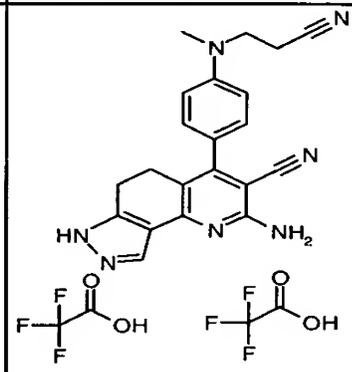
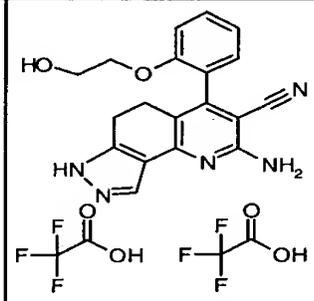
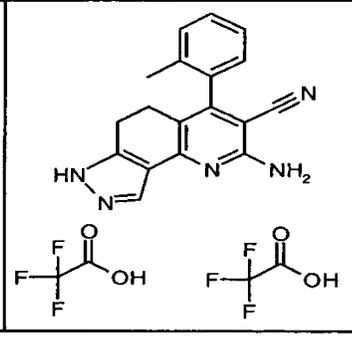
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
261		2-amino-4-[2-(beta-D-glucopyranosyloxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
262		4-[2-(allyloxy)phenyl]-2-amino-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
263		methyl [2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetate bis(trifluoroacetate)	200
264		2-amino-4-(2-ethoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
265		ethyl 4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxylate	200

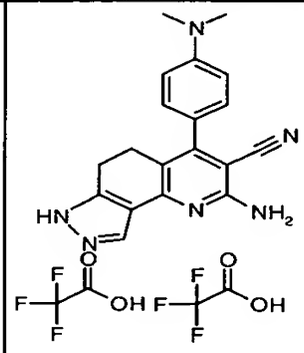
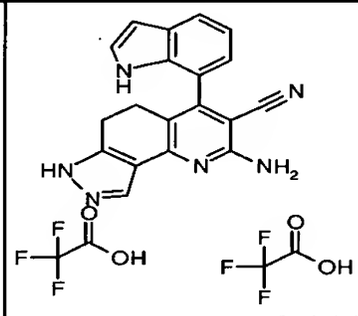
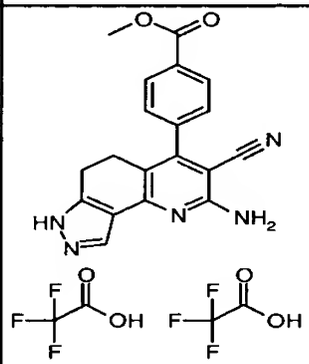
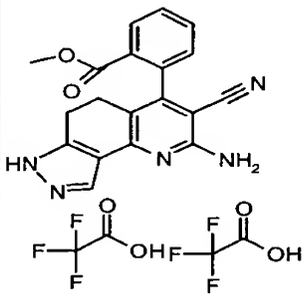
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
266		2-amino-6-methylnicotinonitrile hydrochloride	200
267		2-amino-6-(4-cyanophenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	200
268		2-amino-6-(4-fluorobenzyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	200
269		2-amino-5-(4-fluorophenyl)-4-(2-furyl)-6-methylnicotinonitrile trifluoroacetate	200
270		2-amino-4-(2-furyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200
271		2-amino-4-(2-methylphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile trifluoroacetate	200

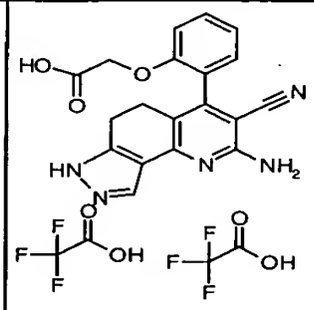
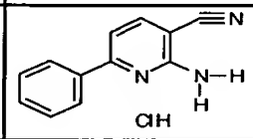
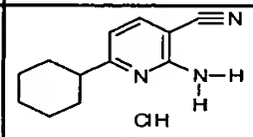
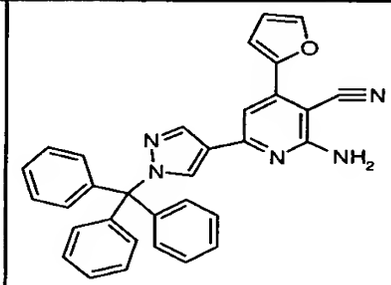
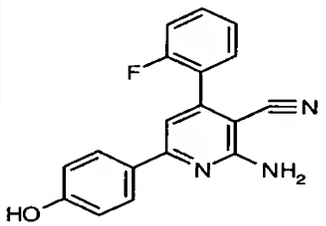
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
272		2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile trifluoroacetate	200
273		2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile	200
274		2-amino-6-(4-methoxyphenyl)-4-(2-methylphenyl)nicotinonitrile trifluoroacetate	200
275		2-amino-4,6-bis(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200
276		2-amino-4-(3-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200
277		2-amino-4-(2-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200

No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
278		2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile bis(trifluoroacetate)	200
279		2-amino-4-(2-furyl)-6-(4-methylphenyl)nicotinonitrile	200
280		2-amino-4-(2-furyl)-6-phenylnicotinonitrile	200
281		6-amino-4-(2-furyl)-2,3'-bipyridine-5-carbonitrile	200
282		2-amino-6-(1,3-benzodioxol-5-yl)-4-(2-furyl)nicotinonitrile	200
283		2-amino-4-isoquinolin-4-yl-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200
284		2-amino-4-(1-benzothien-3-yl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200

No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
285		2-amino-6-(4-methoxyphenyl)-4-thien-3-ylnicotinonitrile trifluoroacetate	200
286		2-amino-4-(3-furyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	200
287		2-amino-6-(4-methoxyphenyl)-4-(1H-pyrrol-2-yl)nicotinonitrile trifluoroacetate	200
288		2-amino-4-(2-furyl)-6-(1H-pyrrol-2-yl)nicotinonitrile	200
289		2'-amino-6'-(4-methoxyphenyl)-3,4'-bipyridine-3'-carbonitrile trifluoroacetate	200
290		2-amino-4-[2-(trifluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200

No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
291		2-amino-4-(2-furyl)-5H-thiochromeno[4,3-b]pyridine-3-carbonitrile trifluoroacetate	200
292		2-amino-4-{4-[(2-cyanoethyl)(methyl)amino]phenyl}-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
293		2-amino-4-[2-(2-hydroxyethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
294		2-amino-4-(2-methylphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200

No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
295		2-amino-4-[4-(dimethylamino)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
296		2-amino-4-(1H-indol-7-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	200
297		methyl 4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	200
298		methyl 2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	200

No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
299		[2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetic acid bis(trifluoroacetate)	200
300		2-amino-6-phenylnicotinonitrile hydrochloride	200
301		2-amino-6-cyclohexylnicotinonitrile hydrochloride	200
302		2-amino-4-(2-furyl)-6-(1-trityl-1H-pyrazol-4-yl)nicotinonitrile	200
303		2-amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile	200

Notes:

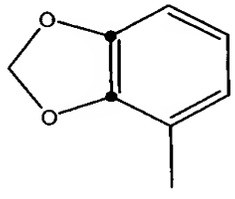
a: The aminocyanopyridine compound may be shown with a solvent, such as, for example, trifluoroacetate, with which it can form a salt. Both the salt and acid forms of the aminocyanopyridine compound are included in the present invention.

b: Compound names generated by ACD/Name software.

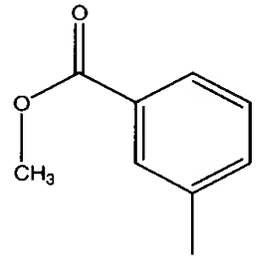
[00044] In another embodiment, the method of the present invention comprises the administering to the subject an aminocyanopyridine compound having the structure shown in formula I, where:

R^1 is selected from the group consisting of -H, methyl, ethyl, propyl, butyl, -(CH_2)COOH, phenyl, pyridyl, dimethylaminoethyl, methoxyethyl, tetramethylaminoethyl, carboxymethyl, and phenylacetyl;

R^2 is selected from the group consisting of -H, methyl, ethyl, propyl, butyl, amino, phenyl, methoxy, carboxy, carboxymethyl, hydroxyethylamino, propylamino, ethylamino, methylamino, methoxyethyl, ethoxyethylamino, aminoethylamino, benzylamino, dimethylaminoethylamino, phthaloaminoethyl, fluorophenyl, difluorophenyl, chlorophenyl, bromophenyl, furyl, carbamylpyrryl, methyl-1,3-isodiazoyl, 1,3-isodiazoyl, 1,3,4-triazoyl, methoxyphenyl, -S(CH_3), tetramethylaminoethyl, acetylaminophenyl, methoxyphenylamino, carboxyphenyl, carboxy-3-isopyrryl, cyanophenyl, cyclopropyl, phenoxyphenyl, pyridyl, dihydroxybromophenyl, difluoromethoxyphenyl, trifluoromethylphenyl, trifluoromethylfluorophenyl, hydroxyphenyl, methylaminomethyl, methylaminoethyl, thiophyl, pyrryl, aminomethyl,



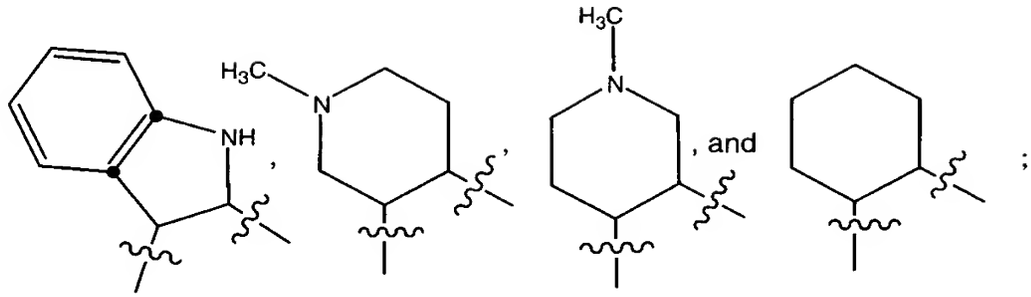
, and



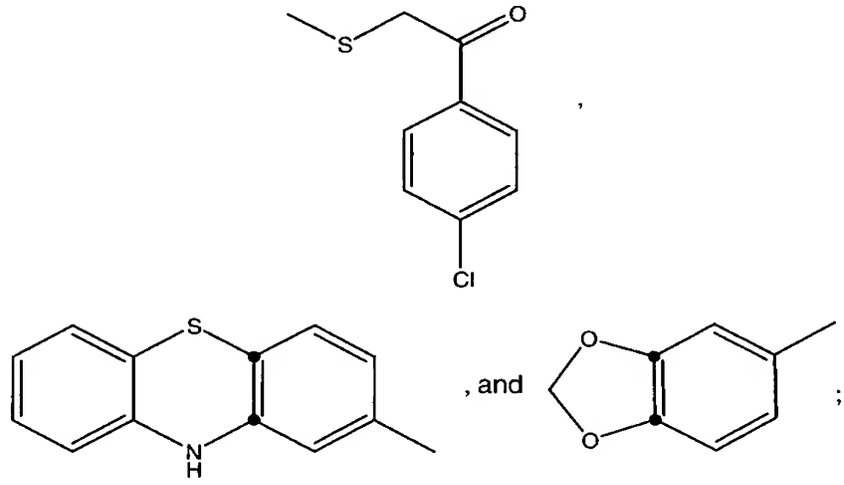
;

R^3 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyano, aminomethyl, phenyl, fluorophenyl, and amino;

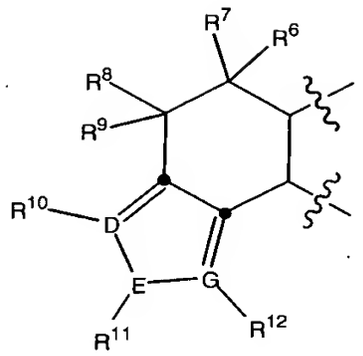
wherein the R^2 and R^3 groups are such that they optionally join to form a ring system selected from the group consisting of:



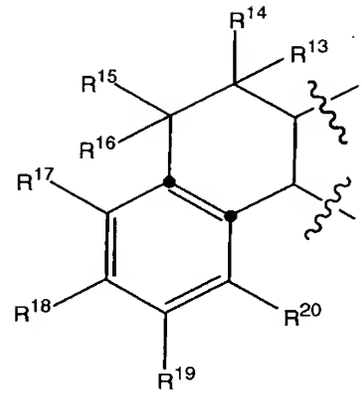
R^4 is selected from the group consisting of -H, methyl, ethyl, propyl, hydroxy, furyl, methylfuryl, methylimidazolyl, phenyl, hydroxyphenyl, carboxyphenyl, pyrazolyl, hydroxy, dihydroxyphenyl, methoxyphenyl, chlorophenyl, bromophenyl, fluorophenyl, dichlorophenyl, dihydroxyborophenyl, thienyl, pyrryl, *N*-methylpyrryl, pyridyl, methylthio, methylsulfonylphenyl, carboethoxyphenyl, methoxy, carbamylphenyl, mercapto, *N*-isoimidazoylphenyl, isopropyl, amino, hydroxynaphthyl, thiazoyl, carboxymethylphenyl, trifluoromethylphenyl, methylphenyl, cyanophenyl, dimethylphenyl, fluorobenzhydryl, methoxyfuryl, aminosulfonylphenyl,



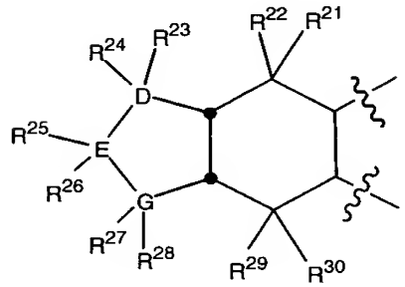
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from the group consisting of:


R7
R6
R8
R9
R10
D
E
G
R11
R12

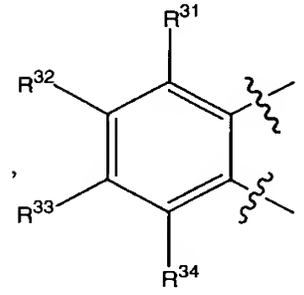
,


R14
R13
R15
R16
R17
R18
R20
R19

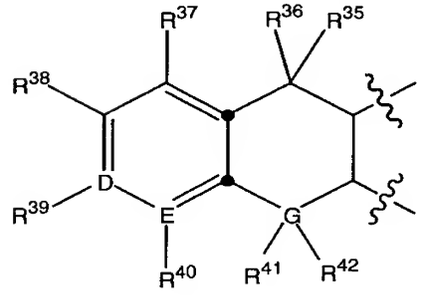
,


R22
R21
R24
R23
D
R25
E
R26
G
R27
R28
R29
R30

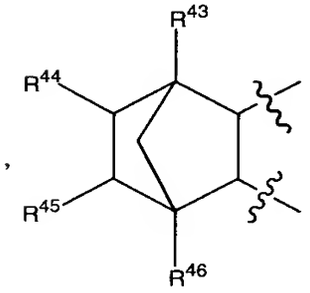
,


R31
R32
R33
R34

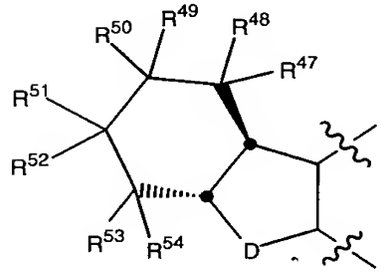
,


R37
R36
R35
R38
D
R39
E
G
R40
R41
R42

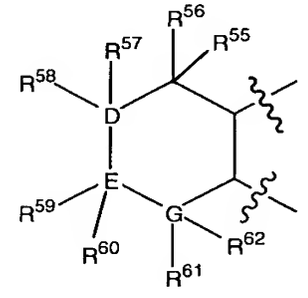
,


R43
R44
R45
R46

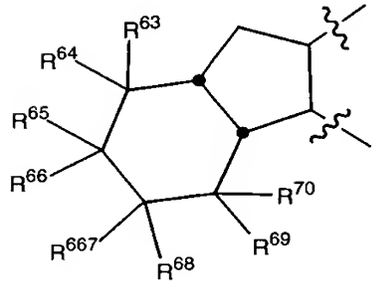
,


R50
R49
R48
R47
R51
R52
R53
R54
D

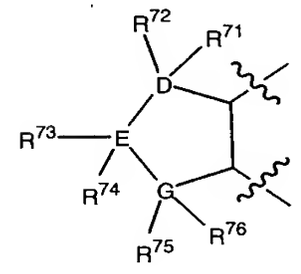
,


R56
R57
R55
R58
D
E
R59
G
R60
R62
R61

,


R63
R64
R65
R66
R70
R667
R69
R68

, and


R72
R71
D
R73
E
R74
G
R75
R76

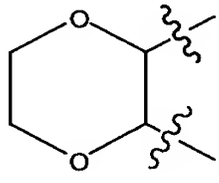
;

D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

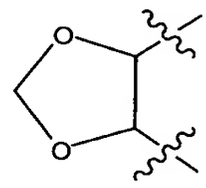
R^5 is selected from the group consisting of -H, and C_1-C_5 alkyl; and wherein the R^1 and R^5 groups can join to form a piperidyl ring;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66}, R^{67}, R^{68}, R^{69}, R^{70} R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present (for example, they can be present when required to balance the valence of the atom to which they are shown as being bound) and are each independently selected from the group consisting of -H, methyl, ethyl, propyl, butyl, isobutyl, amino, nitro, hydroxy, methoxy, ethoxy, propoxy, 2-propenoxy, oxo, carboxy, bromo, chloro, fluoro, trifluoromethyl, chloromethyl, hydroxymethyl, dicyanomethyl, 2-fluorophenyl, 3-fluorophenyl, hydroxyethoxy, ethoxyethoxy, -(CH_2)-O-(C_6H_4)-O-(CH_3), carboxymethoxy, isopropylcarboxymethoxy, isobutylcarboxymethoxy, methylamino, dimethylamino, aminoethoxy, diaminoethoxy, dimethylaminoethoxy, cyanomethoxymethyl, 2-propenoxymethyl, methoxymethyl, isopropoxymethyl, ethoxymethyl, -(CH_2)-O-(CF_2)-CHF_2, isobutoxymethyl, benzoyl, phenyl, *N*-morpholinyl, morpholinylethoxy, pyrrolidylethoxy, *N*-pyrrolidylethoxy, oxo, ethylcarboxy, carboxymethyl - ethyl ester, pyridylmethyl, 4-pyridylmethoxy, 2-pyridylmethyl, and -COO-CH_2-CH_3; and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from the group consisting of:



, and

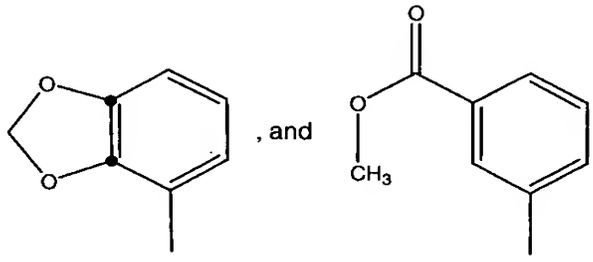


.

[00045] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 200 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is selected from the group consisting of -H, methyl, ethyl, -(CH_2)COOH, and phenyl;

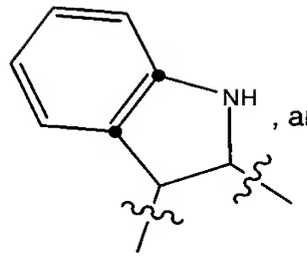
R^2 is selected from the group consisting of -H, methyl, ethyl, amino, phenyl, methoxy, carboxy, hydroxyethylamino, propylamino, ethylamino, methylamino, methoxyethyl, ethoxyethylamino, aminoethylamino, benzylamino, dimethylaminoethylamino, fluorophenyl, difluorophenyl, chlorophenyl, bromophenyl, furyl, carbamylpyrryl, methyl-1,3-isodiazoyl, 1,3-isodiazoyl, 1,3,4-triazoyl, methoxyphenyl, -S(CH_3), acetylaminophenyl, methoxyphenylamino, carboxyphenyl, cyanophenyl, cyclopropyl, phenoxyphenyl, pyridyl, dihydroxybromophenyl, difluoromethoxyphenyl, trifluoromethylphenyl, trifluoromethylfluorophenyl, hydroxyphenyl,



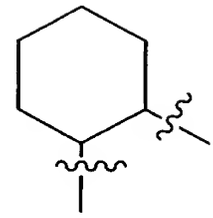
;

R^3 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, cyano, and aminomethyl;

wherein the R^2 and R^3 groups are such that they optionally join to form a ring system selected from the group consisting of:

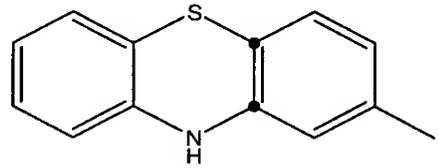


, and



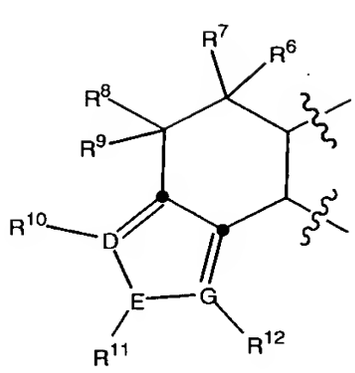
;

R^4 is selected from the group consisting of -H, methyl, ethyl, propyl, hydroxy, furyl, indolyl, methylfuryl, methylimidazolyl, phenyl, hydroxyphenyl, carboxyphenyl, pyrazolyl, hydroxy, dihydroxyphenyl, methoxyphenyl, chlorophenyl, dichlorophenyl, dihydroxyborophenyl, thienyl, pyrryl, *N*-methylpyrryl, pyridyl, methylthio, methylsulfonylphenyl, carboethoxyphenyl, methoxy, carbamylphenyl, *N*-isoimidazoylphenyl, amino, hydroxynaphthyl, thiazoyl, carboxymethylphenyl, aminosulfonylphenyl, and

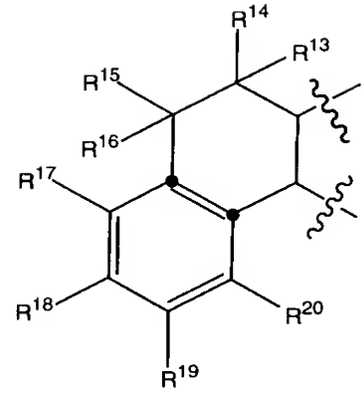


;

wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from the group consisting of:



,



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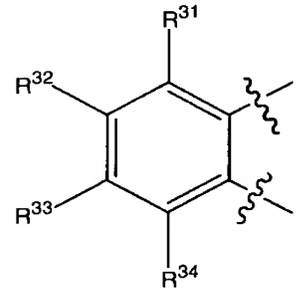

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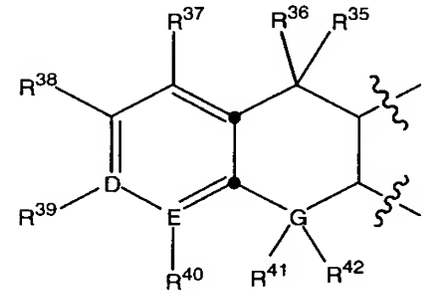
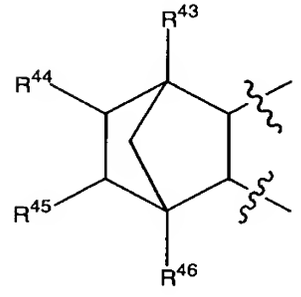
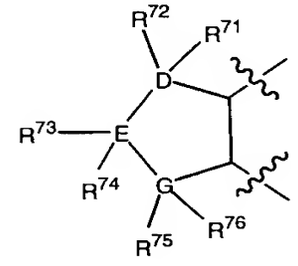


,



, and



;

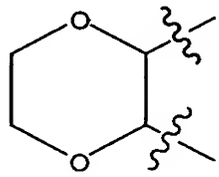
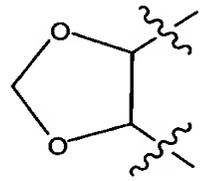
D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

R^5 is selected from the group consisting of -H, and C_1-C_5 alkyl;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present (such as when required to balance the valence of the atom to which they are shown as being bound) and are each independently selected from the group consisting of - H, methyl, ethyl, butyl, amino, nitro, hydroxy, methoxy, ethoxy, oxo, 2-propenoxy, carboxy, bromo, chloro, fluoro, trifluoromethyl,

chloromethyl, hydroxymethyl, dicyanomethyl, hydroxyethoxy, ethoxyethoxy, -(CH_2)-O-(C_6H_4)-O-(CH_3), carboxymethoxy, isopropylcarboxymethoxy, methylamino, dimethylamino, aminoethoxy, diaminoethoxy, cyanomethoxymethyl, methoxymethyl, isopropoxymethyl, ethoxymethyl, -(CH_2)-O-(CF_2)-CHF_2, isobutoxymethyl, phenyl, morpholinylethoxy, pyrrolidylethoxy, *N*-pyrrolidylethoxy, and pyridylmethyl, and

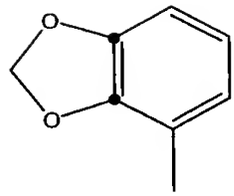
wherein R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from the group consisting of:


, and


[00046] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 100 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is selected from the group consisting of -H, methyl, and ethyl;

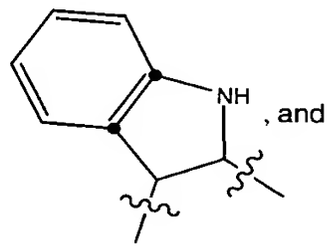
R^2 is selected from the group consisting of -H, methyl, amino, phenyl, methoxy, hydroxyethylamino, propylamino, ethylamino, methylamino, methoxyethyl, ethoxyethylamino, aminoethylamino, benzylamino, dimethylaminoethylamino, fluorophenyl, difluorophenyl, chlorophenyl, bromophenyl, furyl, carbamylpyrryl, methyl-1,3-isodiazoyl, 1,3-isodiazoyl, 1,3,4-triazoyl, methoxyphenyl, -S(CH_3), acetylaminophenyl, methoxyphenylamino, carboxyphenyl, cyanophenyl, cyclopropyl, phenoxyphenyl, pyridyl, dihydroxybromophenyl, difluoromethoxyphenyl, and

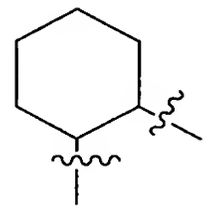


;

R^3 is selected from the group consisting of -H, methyl, ethyl, propyl, isopropyl, and cyano;

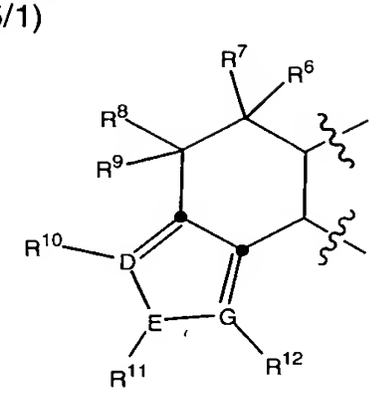
wherein the R^2 and R^3 groups are such that they optionally join to form a ring system selected from the group consisting of :



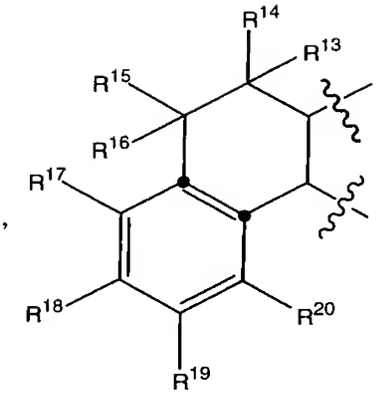
, and

;

R^4 is selected from the group consisting of -H, methyl, ethyl, propyl, hydroxy, furyl, indolyl, methylfuryl, methylimidazolyl, phenyl, hydroxyphenyl, carboxyphenyl, pyrazolyl, hydroxy, dihydroxyphenyl, methoxyphenyl, chlorophenyl, dichlorophenyl, dihydroxyborophenyl, thienyl, pyrryl, *N*-methylpyrryl, pyridyl, methylthio, methylsulfonylphenyl, carboethoxyphenyl, methoxy, carbamylphenyl, amino, and aminosulfonylphenyl;

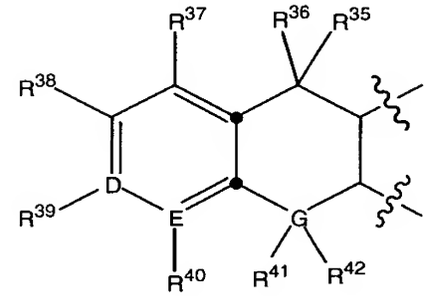
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from:



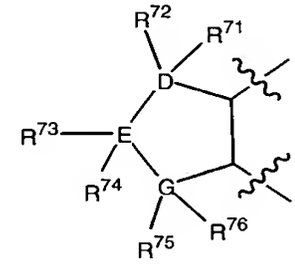
,



,



, and



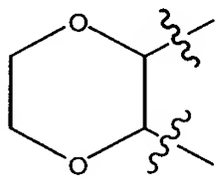
;

D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

R^5 is -H;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present (such as when required to balance the valence of the atom to which they are shown as being bound) and are each independently selected from the group consisting of - H, methyl, ethyl, butyl, amino, nitro, hydroxy, methoxy, ethoxy, oxo, 2-propenoxy, carboxy, bromo, fluoro, trifluoromethyl, chloromethyl, dicyanomethyl, hydroxyethoxy, ethoxyethoxy, -(CH_2)-O-(C_6H_4)-O-(CH_3), carboxymethoxy, isopropylcarboxymethoxy, methylamino, dimethylamino, aminoethoxy, diaminoethoxy, phenyl, morpholinylethoxy, pyrrolidylethoxy, *N*-pyrrolidylethoxy, and pyridylmethyl, and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system consisting of:

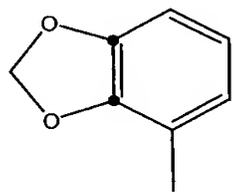


.

[00047] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 50 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R^1 is selected from the group consisting of -H, methyl, and ethyl;

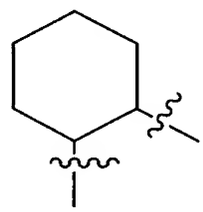
R^2 is selected from the group consisting of -H, methyl, amino, phenyl, methoxy, hydroxyethylamino, propylamino, ethylamino, methylamino, methoxyethyl, ethoxyethylamino, aminoethylamino, benzylamino, dimethylaminoethylamino, fluorophenyl, difluorophenyl, chlorophenyl, bromophenyl, furyl, carbamylpyrryl, methyl-1,3-isodiazoyl, 1,3-isodiazoyl, 1,3,4-triazoyl, methoxyphenyl, -S(CH_3), acetylaminophenyl, methoxyphenylamino, carboxyphenyl, and



;

R^3 is selected from the group consisting of -H, methyl, ethyl, propyl, and isopropyl;

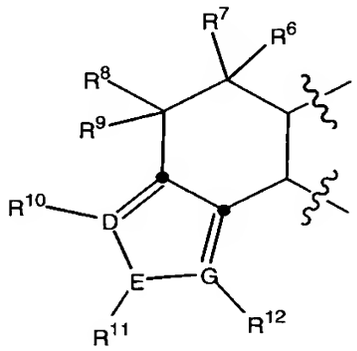
wherein the R^2 and R^3 groups are such that they optionally join to form a ring system consisting of :


;

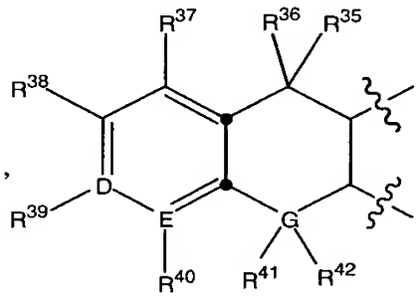
R^4 is selected from the group consisting of -H, methyl, ethyl, propyl, furyl, indolyl, methylfuryl, methylimidazolyl, phenyl, hydroxyphenyl, carboxyphenyl, pyrazolyl, hydroxy, dihydroxyphenyl, methoxyphenyl,

chlorophenyl, dichlorophenyl, dihydroxyborophenyl, thienyl, pyrryl, *N*-methylpyrryl, pyridyl, methylthio, methylsulfonylphenyl, carboethoxyphenyl, and aminosulfonylphenyl;

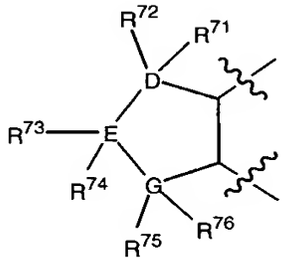
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from:



,



, and



;

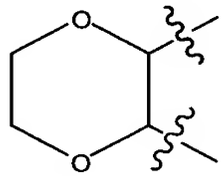
D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

R^5 is -H;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present (such as when required to balance the valence of the atom to which they are shown as being bound) and are each independently selected from the group consisting of - H, methyl, ethyl, butyl, amino, nitro, hydroxy, methoxy, ethoxy, oxo, 2-propenoxy, carboxy, bromo, fluoro, trifluoromethyl, chloromethyl, dicyanomethyl, hydroxyethoxy, ethoxyethoxy, carboxymethoxy, isopropylcarboxymethoxy, methylamino, dimethylamino,

aminoethoxy, diaminoethoxy, morpholinylethoxy, pyrrolidylethoxy, *N*-pyrrolidylethoxy, and pyridylmethyl, and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system consisting of:



[00048] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 20 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

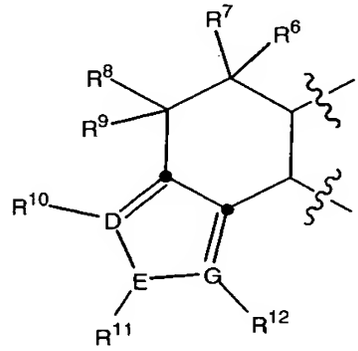
R^1 is -H;

R^2 is selected from the group consisting of amino, phenyl, fluorophenyl, difluorophenyl, furyl, carbamylpyrryl, methyl-1,3-isodiazoyl, 1,3-isodiazoyl, 1,3,4-triazoyl, methoxyphenyl, acetylaminophenyl, methoxyphenylamino, and carboxyphenyl;

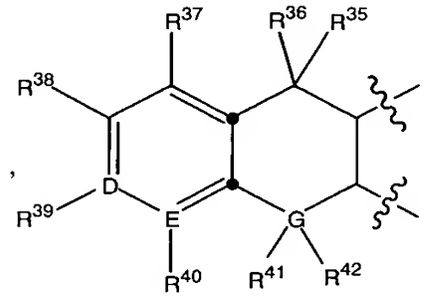
R^3 is selected from the group consisting of -H, methyl, ethyl, and propyl;

R^4 is selected from the group consisting of methyl, ethyl, propyl, furyl, phenyl, hydroxyphenyl, carboxyphenyl, pyrazolyl, hydroxy, dihydroxyphenyl, methoxyphenyl, chlorophenyl, dihydroxyborophenyl, and aminosulfonylphenyl;

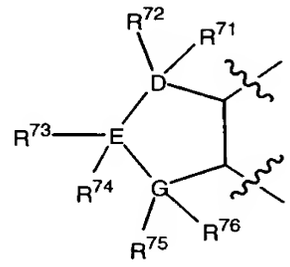
wherein the R^3 and R^4 groups are such that they optionally join to form a ring system selected from the group consisting of:



,



, and



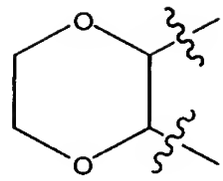
;

D, E and G are each independently selected from the group consisting of carbon, oxygen, sulfur, and nitrogen;

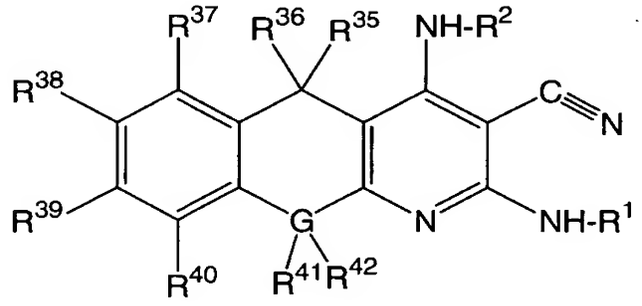
R^5 is -H;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, and R^{76} are each optionally present (such as when required to balance the valence of the atom to which they are shown as being bound) and are each independently selected from the group consisting of - H, amino, nitro, hydroxy, methoxy, ethoxy, oxo, 2-propenoxy, carboxy, bromo, fluoro, trifluoromethyl, chloromethyl, dicyanomethyl, hydroxyethoxy, ethoxyethoxy, carboxymethoxy, isopropylcarboxymethoxy, methylamino, dimethylamino, aminoethoxy, diaminoethoxy, morpholinylethoxy, pyrrolidylethoxy, and pyridylmethyl, and

wherein R^{38} and R^{39} are such that they optionally join to form a ring system consisting of:



[00049] In an embodiment of this invention, the present method can be practiced by the administration of an aminocyanopyridine tricyclic compound having the structure shown in formula II:



II

wherein:

G is selected from the group consisting of - O -, - S -, and -N-;

when G is -O-, R^{41} and R^{42} are absent;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -N-, R^{41} is absent, and R^{42} is -H or C_1-C_4-alkyl;

each of R^1, R^2, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, and R^{40} is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-

C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

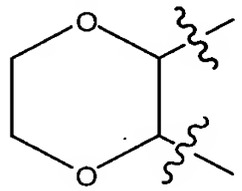
aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

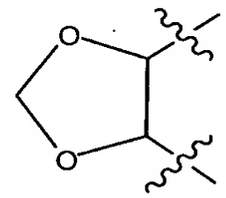
branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl,

where R^{38} and R^{39} are such that they optionally join to form a ring system of the type selected from



, and



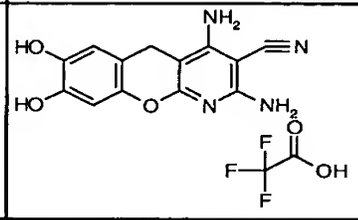
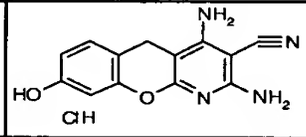
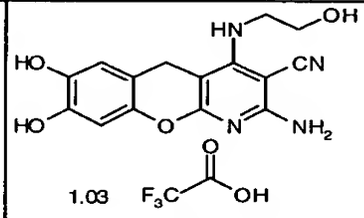
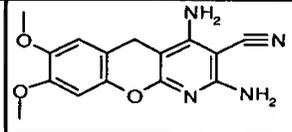
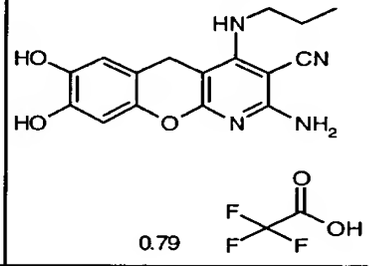
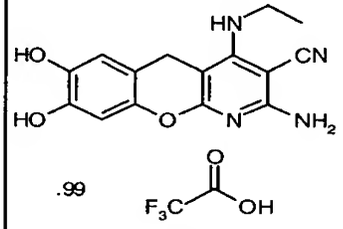
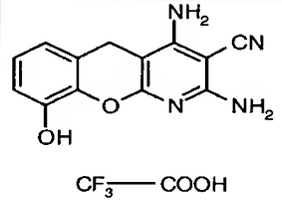
.

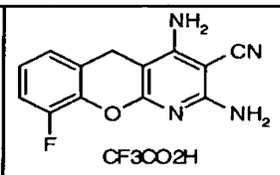
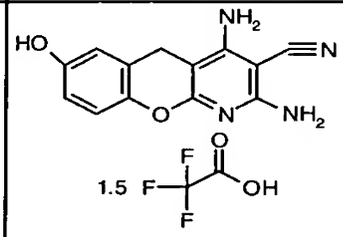
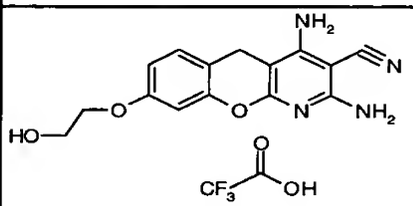
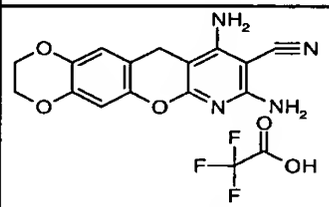
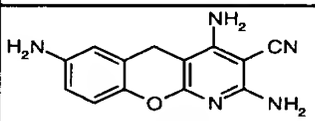
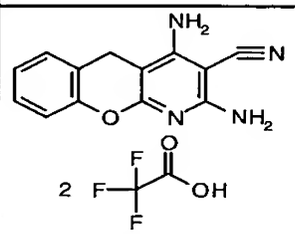
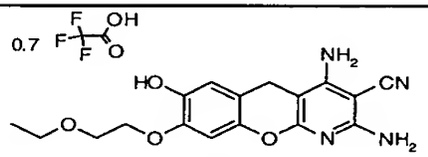
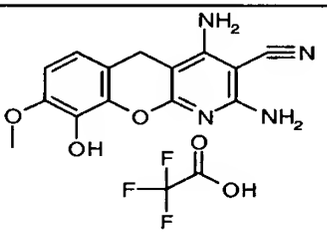
[00050] And where the terms "alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, haloalkoxy, halo, alkylthio, alkylthioalkyl, heterocyclyl, cyclyl, aryl, heteroaryl, cycloaryl, and oxo" have the same meanings as described above.

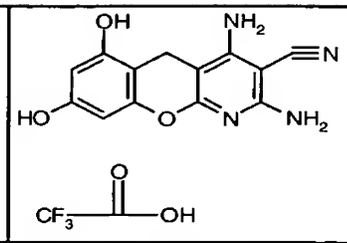
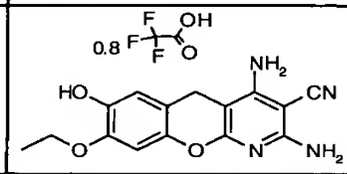
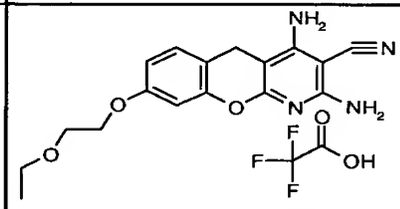
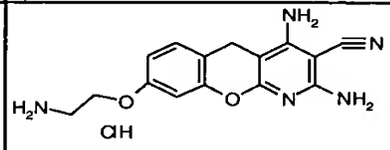
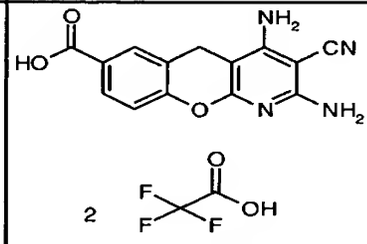
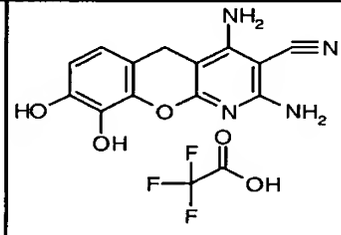
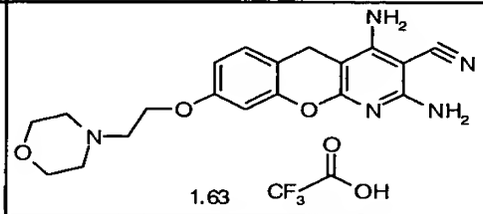
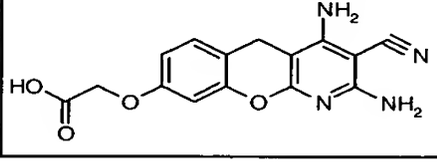
[00051] The tricyclic aminocyanopyridine compounds that are useful in the present invention include benzonapthyridines, pyridochromanes, and pyridothiochromanes.

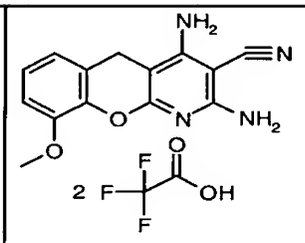
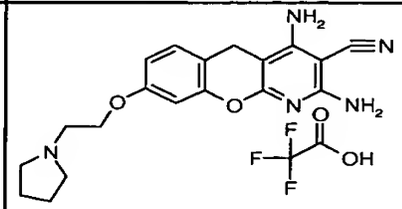
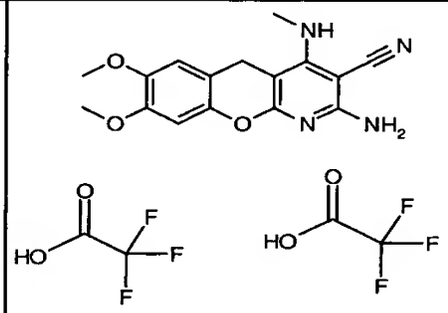
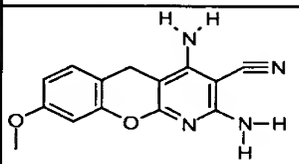
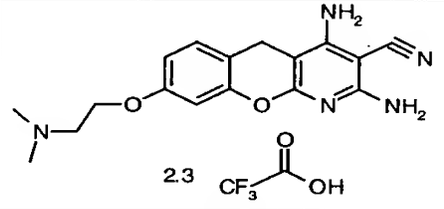
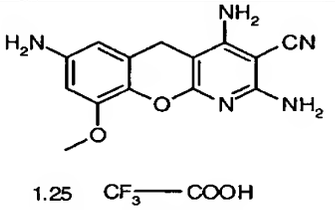
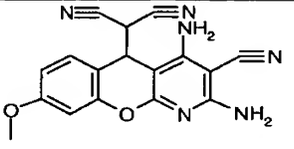
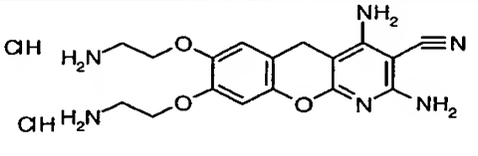
[00052] Examples of tricyclic aminocyanopyridine compounds that are useful as MK-2 inhibitors in the present method are shown in Table II:

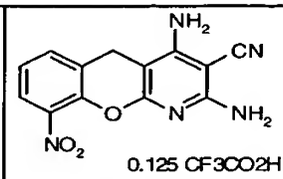
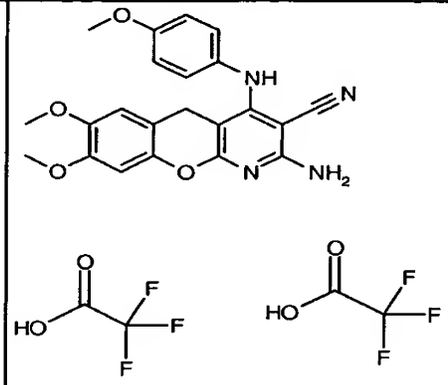
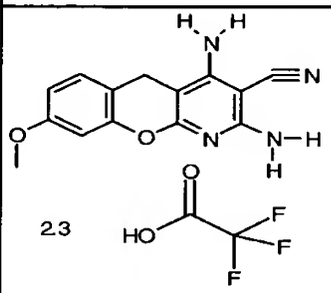
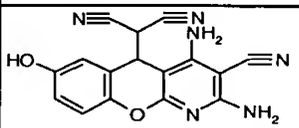
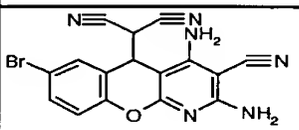
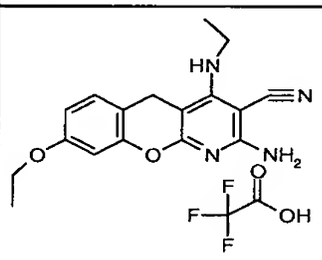
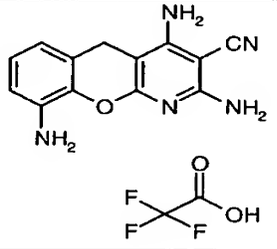
TABLE 2: Tricyclic Aminocyanopyridine MK-2 Inhibitors

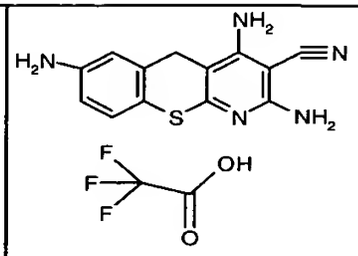
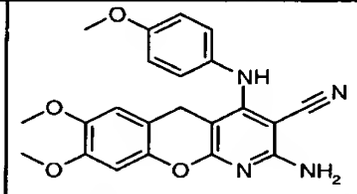
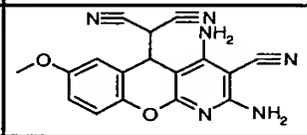
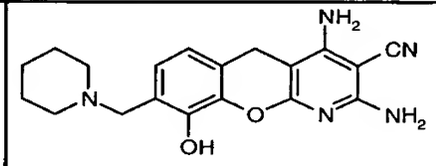
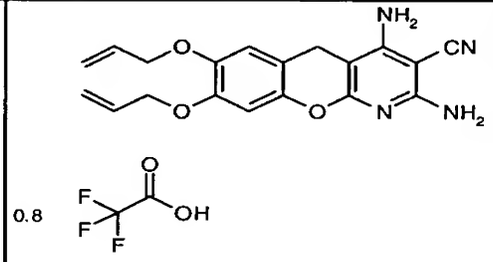
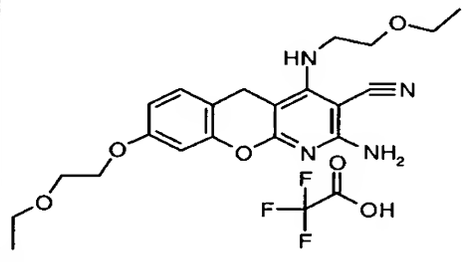
No.	Structure[a]	Compound Name(s)[b]	MK-2 Avg. IC50 (uM)
1		2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.125
2		2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.187
3		2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.237
4		2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.335
5		2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.403
6		2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.419
7		2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.459

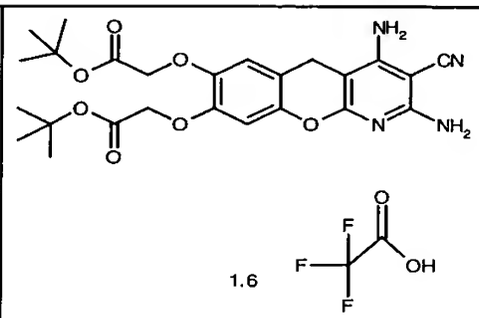
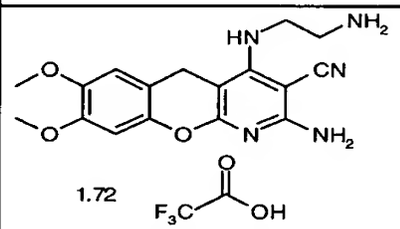
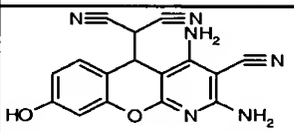
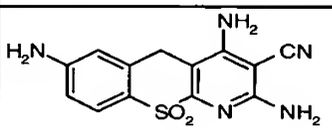
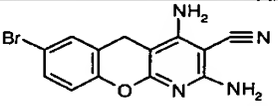
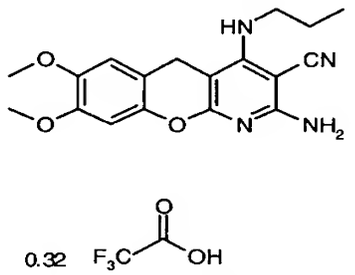
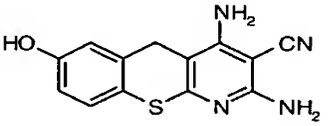
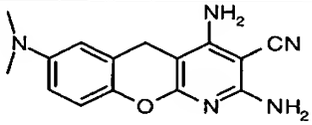
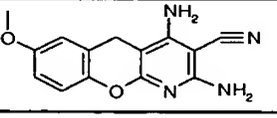
8		2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.471
9		2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.473
10		2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.483
11		8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile trifluoroacetate	0.488
12		2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.514
13		2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.563
14		2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.62
15		2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.682

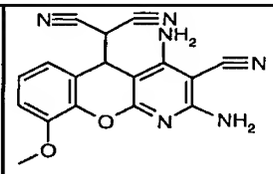
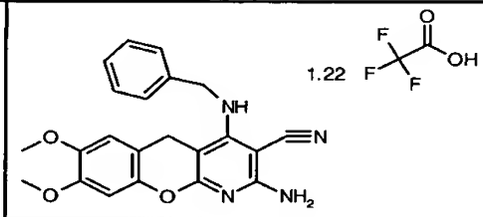
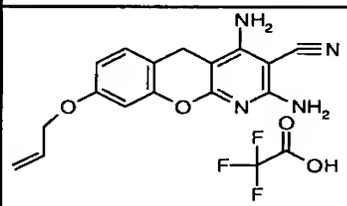
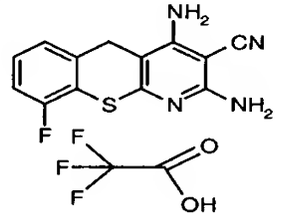
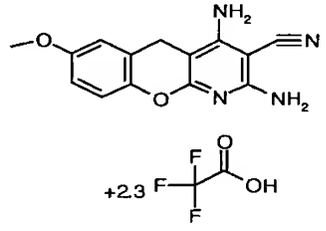
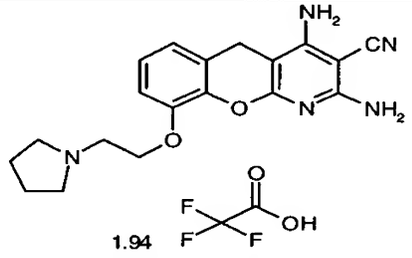
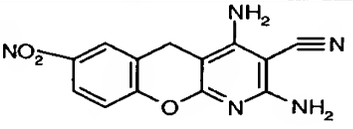
16		2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.694
17		2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.773
18		2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.817
19		2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.82
20		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid trifluoroacetate	0.857
21		2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.857
22		2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.91
23		[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid trifluoroacetate	0.916

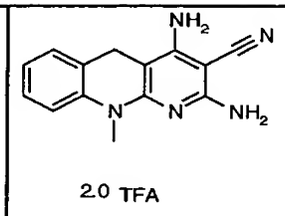
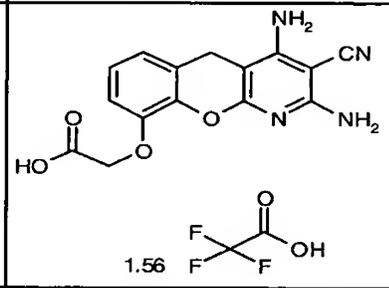
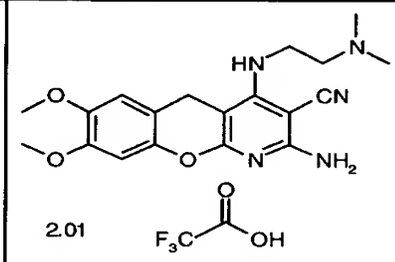
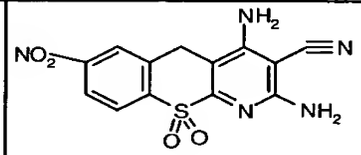
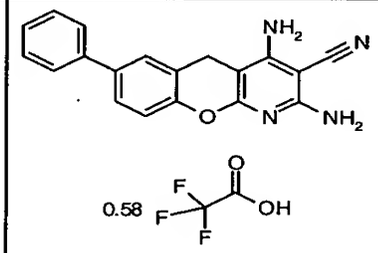
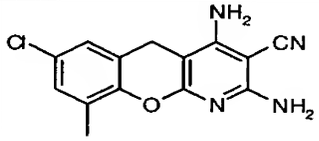
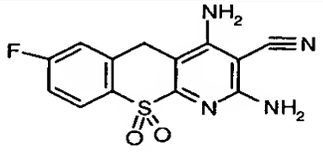
24		2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.37
25		2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.68
26		2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	1.69
27		2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.72
28		2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.75
29		2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.79
30		2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	1.94
31		2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	2.55

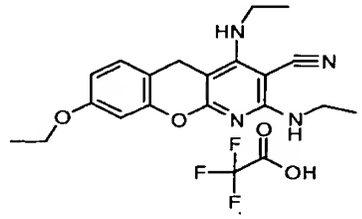
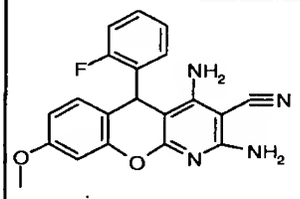
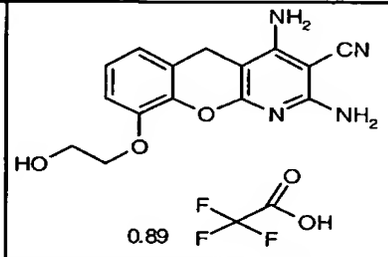
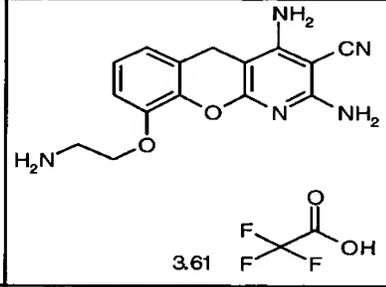
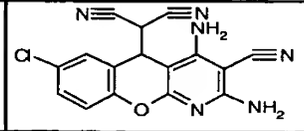
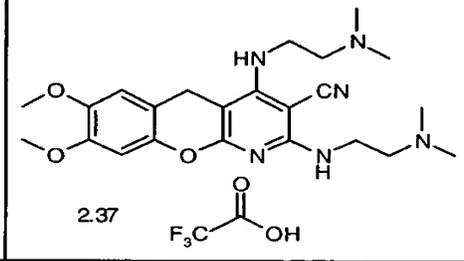
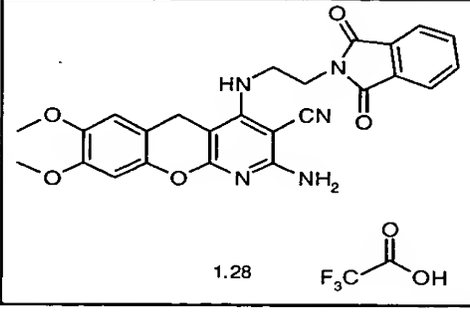
32	 0.125 CF3CO2H	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	2.58
33		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	2.98
34	 2.3	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	3.24
35		2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	3.8
36		2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	4.22
37		2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	4.76
38		2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.01

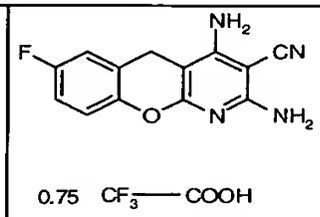
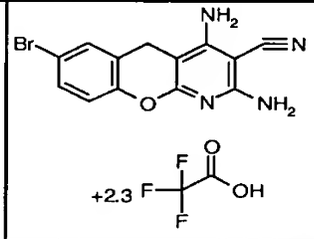
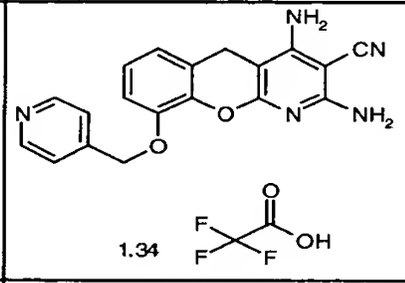
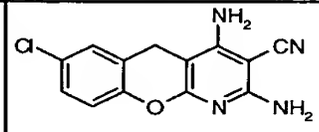
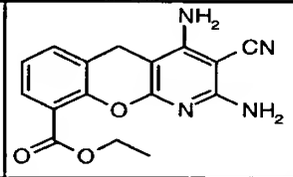
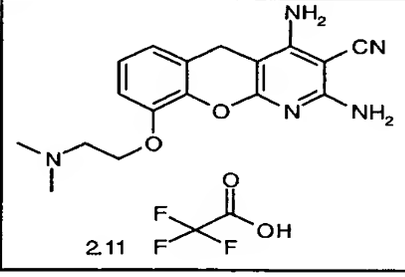
39		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.6
40		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	6.11
41		2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	6.18
42	 2.0 TFA	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	8.28
43	 0.8	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	9.6
44		2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	9.66

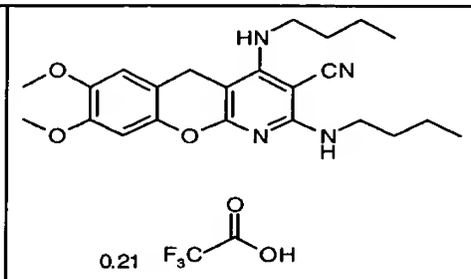
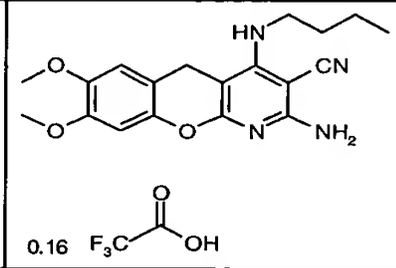
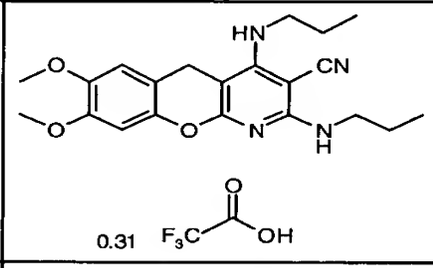
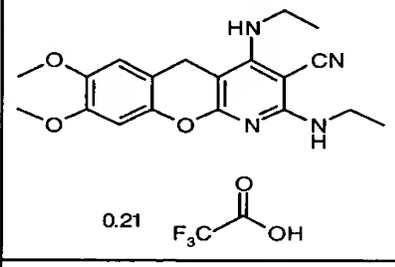
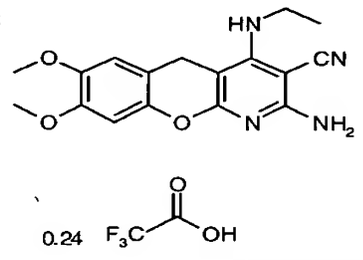
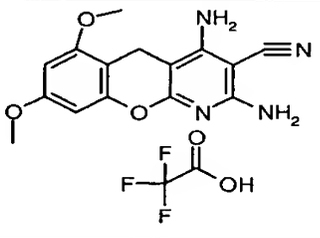
45		tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	10.3
46		2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	11.5
47		2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	12.8
48		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	14.4
49		2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.1
50		2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.6
51		2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	17.4
52		2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	17.6
53		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	19.7

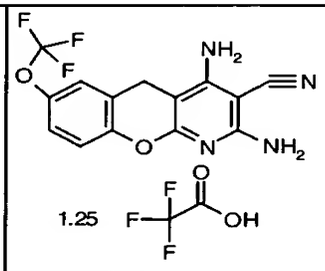
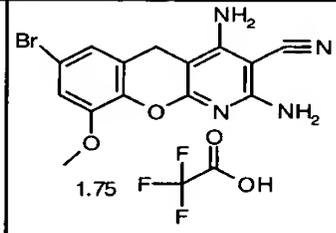
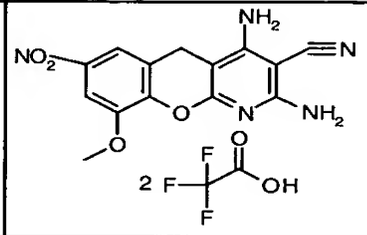
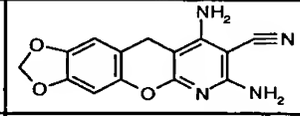
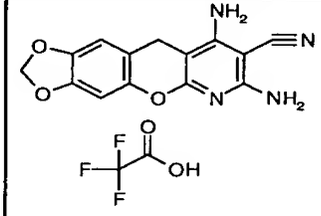
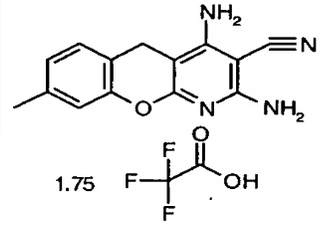
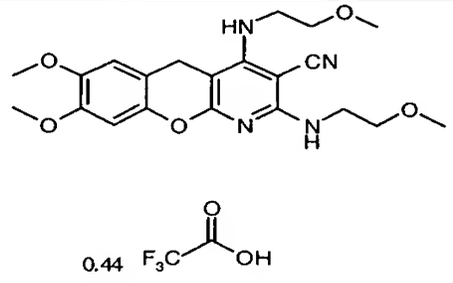
54		2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	21.2
55		2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	27.4
56		8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	33.8
57		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	42.2
58		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	43
59		2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	45.2
60		2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	62.2

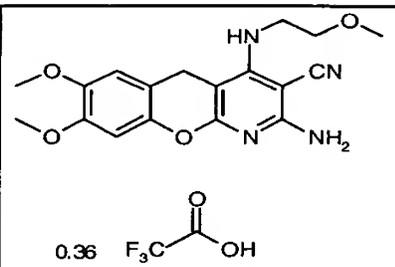
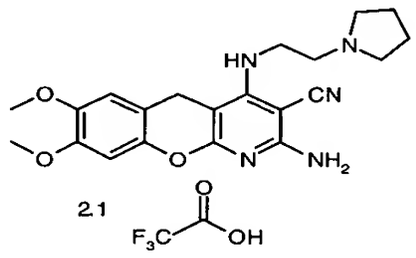
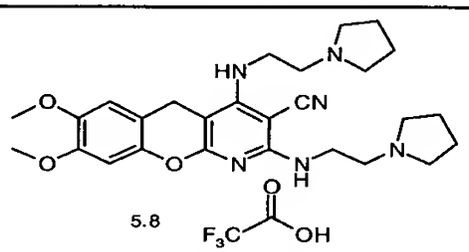
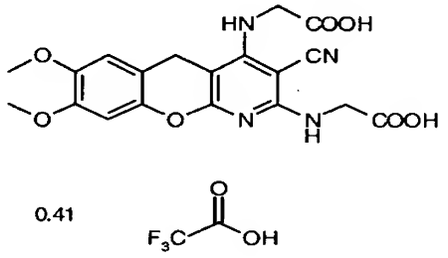
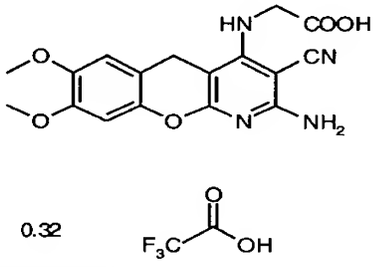
61	 2.0 TFA	2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate	70.1
62	 1.56	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	72.2
63	 2.01	2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	79.1
64		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	80.8
65	 0.58	2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	83.8
66		2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	136
67		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	142

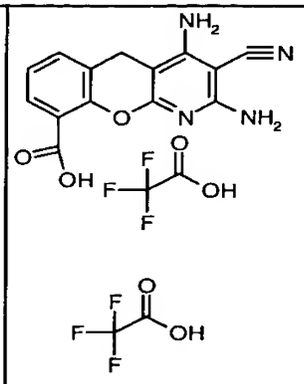
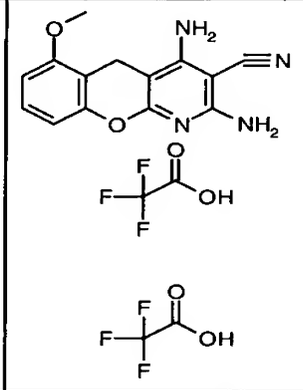
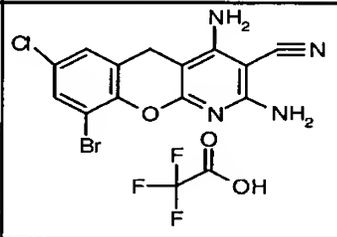
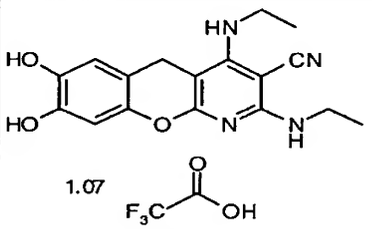
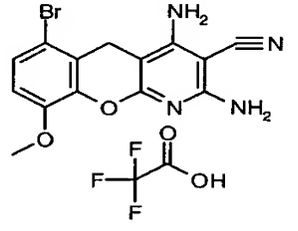
68		8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	148
69		2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	151
70		2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	154
71		2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	161
72		2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	200
73		2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
74		2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

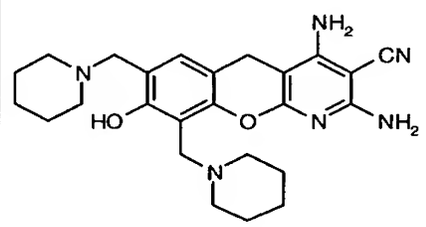
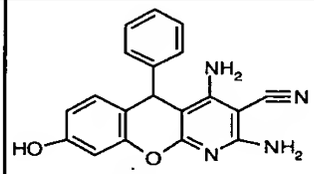
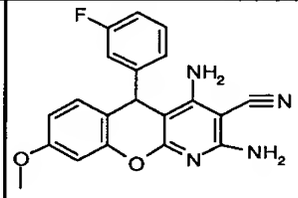
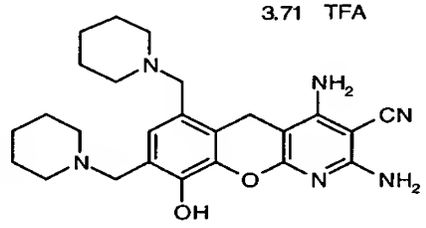
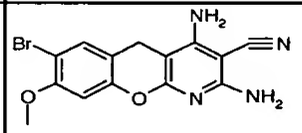
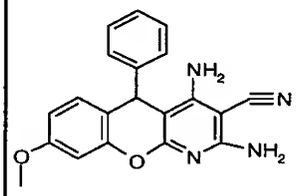
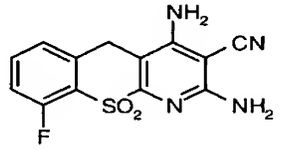
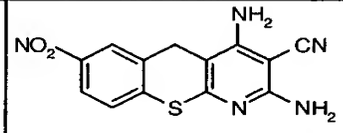
75	 0.75 CF_3—COOH	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
76	 +2.3	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
77	 1.34	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
78	 1.75 CF3CO2H	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
79	 1.25 CF3CO2H	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
80		ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	200
81	 2.11	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

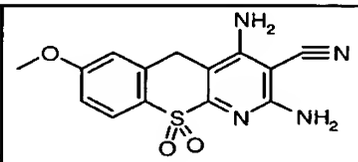
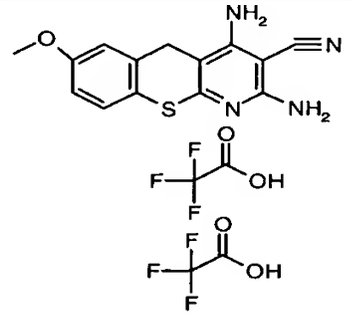
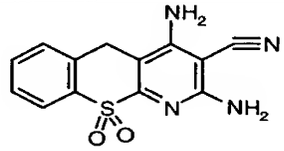
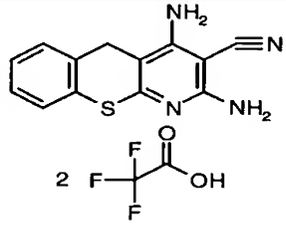
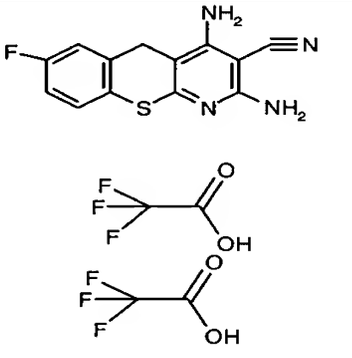
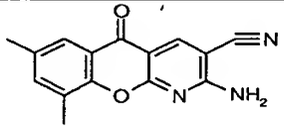
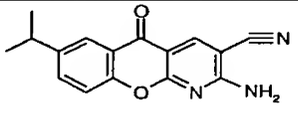
82		2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
83		2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
84		7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
85		2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
86		2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
87		2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

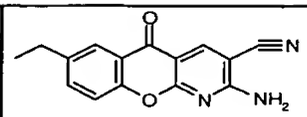
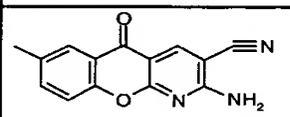
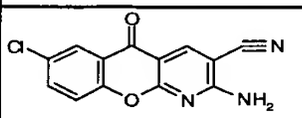
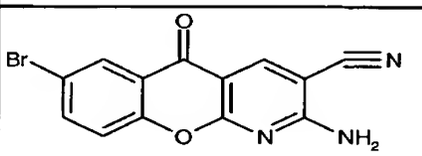
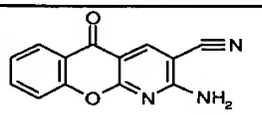
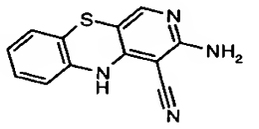
88		2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
89		2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
90		2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
91		7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	200
92		7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile trifluoroacetate	200
93		2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
94		7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

95		2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
96		2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
97		7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
98		2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
99		N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	200

100		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	200
101		2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
102		2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
103		2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
104		2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

105	3.76 TFA 	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
106		2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
107		2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
108	3.71 TFA 	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
109		2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
110		2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
111		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
112		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	200

113		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
114		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
115		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
116		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
117		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
118		2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
119		2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

120		2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
121		2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
122		2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
123		2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
124		2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
125		3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile	200

Notes:

a: The aminocyanopyridine compound may be shown with a solvent, such as, for example, trifluoroacetate, with which it can form a salt. Both the salt and acid forms of the aminocyanopyridine compound are included in the present invention.

b: Compound names generated by ACD/Name software.

[00053] In another embodiment, the present method can be practiced by administering aminocyanopyridine compounds comprising the compound shown in formula II, where:

G is selected from the group consisting of - O -, - S -, and -N-;

when G is -O-, R^{41} and R^{42} are absent;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -N-, R^{41} is absent, and R^{42} is -H or C_1-C_4-alkyl;

R^1 is selected from the group consisting of hydrogen, branched or unbranched alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, arylalkyl, carboxy, carboxyalkyl, hydroxyalkyl, alkylcarboxy, aryl, amino, aminoalkyl, alkylamino, halo, alkylaminoalkyl, alkoxy, alkoxyalkyl, monocyclyl, bicyclyl, polycyclyl, and heterocyclyl;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^{35} is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^{36} is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^{37} is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, or alkylaryl;

R^{38} is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

R^{39} is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the R^{38} and R^{39} groups can join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclylalkyl.

[00054] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound comprising the compound shown in formula II, where:

G is selected from the group consisting of -O-, -S-, and -N-;

when G is -O-, R^{41} and R^{42} are absent;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -N-, R^{41} is absent, and R^{42} is -H or $-CH_3$;

R^1 is selected from the group consisting of hydrogen, ethyl, dimethylaminoethyl, butyl, propyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^2 is selected from the group consisting of hydrogen, hydroxyethyl, propyl, ethyl, methyl, 4-methoxyphenyl, ethoxyethyl, aminoethyl, phenylmethyl, dimethylaminoethyl, phthaloaminoethyl, butyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

R^{35} is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl.

R^{36} is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl;

R^{37} is selected from the group consisting of hydrogen, hydroxy, methoxy, bromo, and 2-pyridomethyl;

R^{38} is selected from the group consisting of hydrogen, hydroxy, methoxy, amino, carboxy, diaminoethoxy, bromo, propoxy, isobutylcarboxymethoxy, dimethylamino, nitro, phenyl, chloro, pyridylmethyl, and fluoro;

R^{39} is selected from the group consisting of hydrogen, hydroxy, methoxy, hydroxyethoxy, ethoxyethoxy, ethoxy, aminoethoxy,

morpholinoethoxy, carboxymethoxy, *N*-pyrrolidylethoxy, dimethylaminoethoxy, pyridylmethyl, 2-propenoxy, and isobutylcarboxymethoxy, where the R^{38} and R^{39} groups optionally join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, fluoro, methoxy, nitro, amino, pyrrolidylethoxy, carboxymethoxy, methyl, hydroxyethoxy, aminoethoxy, 4-pyridylmethoxy, isobutyl, ethylcarboxy, dimethylaminoethoxy, carboxy, bromo, and pyrridylmethyl.

[00055] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 200 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula II, where:

G is selected from the group consisting of -O- and -S-;

when G is -S-, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -O-, R^{41} and R^{42} are absent;

R^1 is selected from the group consisting of hydrogen, and C_1-C_2 alky;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, amino C_1-C_2 alkyl, phenyl C_1-C_2 alkyl, and di C_1-C_2 alkylamino C_1-C_2 alkyl;

R^{35} and R^{36} are each independently selected from the group consisting of hydrogen, dicyano C_1-C_2 alkyl, and halophenyl;

R^{37} is selected from the group consisting of hydrogen, and hydroxy;

R^{38} is selected from the group consisting of hydrogen, hydroxy, C_1 - C_3 alkoxy, amino, nitro, carboxy, diamino C_1 - C_2 alkoxy, halo, propenoxy, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, di C_1 - C_2 alkylamino, and phenyl;

R^{39} is selected from the group consisting of hydrogen, hydroxy, C_1 - C_3 alkoxy, hydroxy C_1 - C_2 alkoxy, C_1 - C_2 alkoxy C_1 - C_2 alkoxy, amino C_1 - C_2 alkoxy, morpholino C_1 - C_2 alkoxy, carboxyl C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkoxy, di C_1 - C_2 alkylamino C_1 - C_2 alkoxy, pyrrolidyl C_1 - C_2 alkyl, iso C_3 - C_4 alkylcarboxy C_1 - C_2 alkoxy, and 2-propenoxy,

where the R^{38} and R^{39} groups optionally join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkyl, C_1-C_2 alkoxy, nitro, amino, pyrrolidyl C_1-C_2 alkoxy, carboxy C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, and amino C_1-C_2 alkoxy.

[00056] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 100 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula II, where:

G is selected from the group consisting of -O- and -S-;

when G is sulfur, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -O-, R^{41} and R^{42} are absent;

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1 - C_3 alkyl, hydroxy C_1 - C_2 alkyl, C_1 - C_2 alkoxyphenyl, C_1 - C_2 alkoxy C_1 - C_2 alkyl, amino C_1 - C_2 alkyl, phenyl C_1 - C_2 alkyl, and di C_1 - C_2 alkylamino C_1 - C_2 alkyl;

R^{35} and R^{36} are each independently selected from the group consisting of hydrogen, and dicyano C_1 - C_2 alkyl.

R^{37} is selected from the group consisting of hydrogen, and hydroxy;

R^{38} is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, nitro, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, di C_1-C_2 alkylamino, and phenyl;

R^{39} is selected from the group consisting of hydrogen, hydroxy, C_1 - C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

wherein the R^{38} and R^{39} groups optionally join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkoxy, nitro, amino, pyrrolidyl C_1-C_2 alkoxy, and carboxy C_1-C_2 alkoxy.

[00057] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides an IC_{50} of less than about 50 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula II, where:

G is selected from the group consisting of -O- and -S-;

when G is sulfur, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -O-, R^{41} and R^{42} are absent;

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, amino C_1-C_2 alkyl, and phenyl C_1-C_2 alkyl;

R^{35} and R^{36} are each independently selected from the group consisting of hydrogen, and dicyano C_1-C_2 alkyl.

R^{37} is selected from the group consisting of hydrogen, and hydroxy;

R^{38} is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and di C_1-C_2 alkylamino;

R^{39} is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

where the R^{38} and R^{39} groups optionally join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, halo, C_1-C_2 alkoxy, nitro, amino, and pyrrolidyl C_1-C_2 alkoxy.

[00058] In another embodiment, the present method can be practiced by the administration of an aminocyanopyridine compound that provides

an IC_{50} of less than about 20 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula II, where:

G is selected from the group consisting of -O- and -S-;

when G is sulfur, R^{41} and R^{42} are optionally absent, or are oxo;

when G is -O-, R^{41} and R^{42} are absent;

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, C_1-C_3 alkyl, hydroxy C_1-C_2 alkyl, C_1-C_2 alkoxyphenyl, C_1-C_2 alkoxy C_1-C_2 alkyl, and amino C_1-C_2 alkyl;

R^{35} and R^{36} are each independently selected from the group consisting of hydrogen, and dicyanoethyl;

R^{37} is selected from the group consisting of hydrogen, and hydroxy;

R^{38} is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, amino, carboxy, diamino C_1-C_2 alkoxy, halo, 2-propenoxy, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and di C_1-C_2 alkylamino;

R^{39} is selected from the group consisting of hydrogen, hydroxy, C_1-C_2 alkoxy, hydroxy C_1-C_2 alkoxy, C_1-C_2 alkoxy C_1-C_2 alkoxy, amino C_1-C_2 alkoxy, morpholino C_1-C_2 alkoxy, carboxyl C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkoxy, di C_1-C_2 alkylamino C_1-C_2 alkoxy, pyrrolidyl C_1-C_2 alkyl, iso C_3-C_4 alkylcarboxy C_1-C_2 alkoxy, and 2-propenoxy;

where the R^{38} and R^{39} groups optionally join to form a six membered heterocyclic ring; and

R^{40} is selected from the group consisting of hydrogen, hydroxy, halo, methoxy, nitro, and amino.

[00059] Examples of aminocyanopyridine MK-2 inhibitor compounds that can be used in the present method include, without limitation, the following:

2-amino-4-(2-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,

2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,

2-amino-4-(2,3-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile,
2-amino-3-cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid,
4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxamide,
2-amino-4-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-6-(2-furyl)-4-(1-methyl-1H-imidazol-4-yl)nicotinonitrile,
8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile,
2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2,6-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile, 2-amino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoic acid,
2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile,
2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile,
2-amino-3-cyano-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid,
2-amino-6-(3-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile,
2-amino-6-(2-furyl)-4-(1H-imidazol-4-yl)nicotinonitrile,
2-amino-4-(2,4-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
4,6-diamino-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-furyl)-6,8-dihydro-5H-pyrrolo[3,4-h]quinoline-3-carbonitrile,
4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoic acid,
2-amino-4-(2-furyl)-5,6-dihydro-1,8-phenanthroline-3-carbonitrile,
2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile,
2-amino-4-(1-methyl-1H-imidazol-4-yl)-6-phenylnicotinonitrile,

2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile,
4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoic acid,
2-amino-4-(3-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile,
N-{4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenyl}methanesulfonamide,
2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrrolo[2,3-h]quinoline-3-carbonitrile,
2-amino-4-(1H-imidazol-5-yl)-6-phenylnicotinonitrile,
2-amino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(1H-imidazol-5-yl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile,
2-amino-4-(2-furyl)-6-(1H-pyrazol-4-yl)nicotinonitrile,
2-amino-4-(4-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2,5-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(4-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
4,6-diamino-2-(chloromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(1H-imidazol-4-yl)-6-phenylnicotinonitrile,
4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzenesulfonamide,
4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenylboronic acid,
2-amino-6-(4-methoxyphenyl)-4-(4H-1,2,4-triazol-3-yl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-(3-furyl)nicotinonitrile,
2-amino-6-(2-furyl)-4-(methylthio)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile,
8-amino-6-(2-furyl)-4,5-dihydro-2H-pyrazolo[4,3-h]quinoline-7-carbonitrile,
2-amino-4-(2-bromophenyl)-6-(2-furyl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile,
2-amino-4-phenyl-6-thien-2-ylnicotinonitrile,

2-amino-4-(3-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-7-methyl-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-fluorophenyl)-6-(1H-pyrrol-2-yl)nicotinonitrile,
2-amino-4-(2-furyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-3-yl)nicotinonitrile,
3-amino-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile,
N-[4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenyl]acetamide,
6-amino-4-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]-*N*-(tert-butyl)benzenesulfonamide,
4,6-diamino-2-ethyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
6-amino-4-(2-furyl)-2,4'-bipyridine-5-carbonitrile, 2,4-diamino-6-(methylthio)nicotinonitrile,
3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid,
2-amino-6-(4-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile,
2-amino-4-(1,3-benzodioxol-4-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
4,6-diamino-2-methyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(1H-imidazol-5-yl)-6-[4-(methylsulfonyl)phenyl]nicotinonitrile,
2,4-diaminoquinoline-3-carbonitrile,
2,8-diamino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4,6-di(2-furyl)nicotinonitrile,
4,6-diamino-2-butyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
ethyl 4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoate,
2,4-diamino-6-methoxynicotinonitrile,
2-amino-4-methylnicotinonitrile,

2-amino-4-(4-cyanophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-cyclopropyl-6-methylnicotinonitrile,
2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-2-yl)nicotinonitrile,
2-amino-4-(2-chlorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-6-(2-furyl)-4-(4-phenoxyphenyl)nicotinonitrile,
2-amino-4-pyridin-3-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-6-{[2-(4-chlorophenyl)-2-oxoethyl]thio}-4-(2-furyl)pyridine-3,5-dicarbonitrile,
4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid,
2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-4-yl)nicotinonitrile,
4-(6-amino-5-cyano-4-phenylpyridin-2-yl)-*N*-(tert-butyl)benzenesulfonamide,
2-amino-4-methoxynicotinonitrile,
4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]benzoic acid,
4,6-diamino-2-[(4-methoxyphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile,
4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]-*N*-(tert-butyl)benzenesulfonamide,
(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,
3-Pyridinecarbonitrile, 2-Amino-4-Methylm
2-amino-6-(2-furyl)nicotinonitrile,
2-amino-4-(2-furyl)-6-(3-hydroxyphenyl)nicotinonitrile,
4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzamide,
2-amino-4-(2-furyl)-7-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile,
2-amino-4-pyridin-4-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(3-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile,

2-amino-4-[2-(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-6-thien-3-ylnicotinonitrile,
2-amino-4-(3-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile,
2-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid,
2,4-diamino-6-propylpyridine-3,5-dicarbonitrile,
4,6-diamino-2-[(prop-2-ynyloxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
4,6-diamino-2-(hydroxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-6-(2-furyl)-4-[4-(trifluoromethyl)phenyl]nicotinonitrile,
5-amino-7-methylthieno[3,2-b]pyridine-6-carbonitrile,
2-amino-4-(2-furyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
N-[3-cyano-4-(2-fluorophenyl)-6-(2-furyl)pyridin-2-yl]glycine,
2-[(allyloxy)methyl]-4,6-diamino-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-furyl)-6-methyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
4,6-diamino-2-(methoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile,
2-amino-4-(2-furyl)-6-[4-(1H-imidazol-1-yl)phenyl]nicotinonitrile,
2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)nicotinonitrile,
2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-3-carbonitrile,
4,6-diamino-2-(isopropoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
3-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenylboronic acid,
4,6-diamino-2-(ethoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(4-bromophenyl)-6-(2-furyl)nicotinonitrile,
4,6-diamino-2-[(1,1,2,2-tetrafluoroethoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-[2-fluoro-4-(trifluoromethyl)phenyl]-6-(2-furyl)nicotinonitrile,

2-amino-4-(2-methoxyphenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-fluorophenyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
3,6-diamino-4-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile,
6-amino-4-(2-furyl)-2,2'-bipyridine-5-carbonitrile,
2-amino-4-(2-furyl)-6-(8-hydroxy-1-naphthyl)nicotinonitrile,
4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid,
2-amino-6-(3,4-dichlorophenyl)-4-(2-furyl)nicotinonitrile,
2-amino-4-(2-furyl)-6-(10H-phenothiazin-2-yl)nicotinonitrile,
sodium 2-amino-3-cyano-4-quinolinecarboxylate,
2-anilino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
2-amino-4-(3-fluorophenyl)-6-(2-furyl)nicotinonitrile,
2-amino-4-(4-fluorophenyl)-6-(2-furyl)nicotinonitrile,
4,6-diamino-2-(tert-butoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-furyl)-6-(1,3-thiazol-2-yl)nicotinonitrile,
4-(2-fluorophenyl)-6-(2-furyl)-2-piperidin-1-ylnicotinonitrile,
2-amino-6-(4-chlorophenyl)-4-(2-furyl)nicotinonitrile,
2-amino-6-(4-hydroxyphenyl)-4-(2-methoxyphenyl)nicotinonitrile,
2-amino-6-(2-furyl)-4-(2-hydroxyphenyl)nicotinonitrile,
methyl 3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate,
2-amino-4-(2-chlorophenyl)-6-(5-methyl-2-furyl)nicotinonitrile,
3,6-diamino-2-benzoylthieno[2,3-b]pyridine-5-carbonitrile,
methyl 4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoate,
2-aminonicotinonitrile,
2-amino-4-(2-furyl)-8-{[2-(trimethylsilyl)ethoxy]methyl}-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
3-amino-5H-pyrido[4,3-b]indole-4-carbonitrile,

2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid,
2-amino-6-(4-methoxyphenyl)-4-phenylnicotinonitrile,
2-amino-4-(2-furyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile,
2-amino-4-(2-furyl)-6-isobutylnicotinonitrile,
2-amino-6-benzyl-4-(2-furyl)nicotinonitrile,
2-amino-4-(2-furyl)-6-methyl-5-phenylnicotinonitrile,
2-amino-4-(2-furyl)-6-[4-(trifluoromethoxy)phenyl]nicotinonitrile,
2-amino-4-(2-furyl)-6-propyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile,
2-amino-4-(2-furyl)benzo[h]quinoline-3-carbonitrile,
2-amino-6-(4-methoxyphenyl)-4-thien-2-ylnicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-tetrahydrofuran-2-ylnicotinonitrile,
ethyl 6-amino-5-cyano-4-(2-furyl)pyridine-2-carboxylate,
2-amino-4-(2-furyl)-9-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-8-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-8,9-dimethoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-7-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-7,9-dimethyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,
ethyl 4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoate,
2-amino-6-(3-bromophenyl)-4-(2-furyl)nicotinonitrile,
2-amino-4-(2-furyl)-6-[4-(trifluoromethyl)phenyl]nicotinonitrile,
2-amino-4-(2-furyl)-6-[3-(trifluoromethyl)phenyl]nicotinonitrile,
2-amino-4-(2-furyl)-6-[4-(methylsulfonyl)phenyl]nicotinonitrile,
4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
4,6-diamino-3-phenyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
4,6-diamino-3-vinyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-fluorophenyl)-5-methyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,

3-amino-1-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile,
2-amino-4-(2-fluorophenyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile,
2-amino-4-[2-(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-(benzylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
2-amino-4-(2-furyl)-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile,
2-amino-4-(2-furyl)-5H-indeno[1,2-b]pyridine-3-carbonitrile,
3-amino-1-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile,
2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile,
2-amino-4-(2-thienyl)-5,6,7,8-tetrahydro-3-quinolinecarbonitrile,
2-amino-4-(3-fluorophenyl)-5,6,7,8-tetrahydro-3-quinolinecarbonitrile,
2-(1-piperidinyl)-6-(2-thienyl)-4-(trifluoromethyl)nicotinonitrile,
2-(dimethylamino)-6-(2-thienyl)-4-(trifluoromethyl)nicotinonitrile,
3-Quinolinecarbonitrile,
2-amino-4-methyl- or 2-amino-4-methyl-3-quinolinecarbonitrile,
2-amino-4-(4-methoxyphenyl)-6-(2-thienyl)nicotinonitrile,
2-amino-6-cyclopropyl-4-(2-methoxyphenyl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-phenylnicotinonitrile,
(4bS,8aR)-2,4-diamino-4b,5,6,7,8,8a-hexahydro[1]benzofuro[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(2-fluorophenyl)-5,5-dimethyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
3-amino-1,6-dimethyl-5,6,7,8-tetrahydro-2,6-naphthyridine-4-carbonitrile,
3-amino-1,7-dimethyl-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile,
2-amino-4-(2-fluorophenyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,

2-amino-4-(2-fluorophenyl)-5-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,

4,6-diamino-2-(morpholin-4-ylmethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,

ethyl (4,6-diamino-5-cyano-2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate,

2-amino-4-(2-methoxyphenyl)-6-(5-methyl-2-furyl)nicotinonitrile,

2-amino-6-methyl-4-(4-nitrophenyl)nicotinonitrile,

2-amino-4-(3,4-dimethoxyphenyl)-6-(5-methyl-2-furyl)nicotinonitrile,

2,4-diamino-6-[(4-methoxyphenyl)thio]nicotinonitrile,

4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,

4,6-diamino-3-phenyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,

4,6-diamino-2-[(2-methylphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile,

2-amino-4-(2-furyl)-6-(4-methoxyphenyl)nicotinonitrile,

2-amino-4-(3-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile,

2-amino-4-(4-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile,

2-amino-9-ethyl-9H-pyrido[2,3-b]indole-3-carbonitrile,

2-amino-6-isobutyl-4-(4-methylphenyl)nicotinonitrile,

1-(2-furyl)-3-[(3-hydroxypropyl)amino]-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile,

2-azepan-1-yl-6-(4-fluorophenyl)-4-phenylnicotinonitrile,

2-amino-6-tert-butyl-4-(4-methylphenyl)nicotinonitrile,

2-amino-4-(4-bromophenyl)-6-methylnicotinonitrile,

2-amino-4-thien-2-yl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile,

2-amino-4-(4-chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carbonitrile,

2-(allylamino)-5-amino-7-(4-bromophenyl)thieno[3,2-b]pyridine-3,6-dicarbonitrile,

2-amino-4-pyridin-3-yl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile,
2-amino-4-(4-bromophenyl)-6-tert-butylnicotinonitrile,
1-(2-furyl)-3-morpholin-4-yl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile,
2-amino-4-(4-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile,
2-amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile,
2-amino-6-isobutyl-4-(4-methoxyphenyl)nicotinonitrile,
4,6-diamino-2-oxo-1-phenyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile,
2-amino-4-(2-methoxyphenyl)-5,6-dimethylnicotinonitrile,
2-(dimethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
2-(dimethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
4-(2-fluorophenyl)-6-(2-furyl)-2-(methylamino)nicotinonitrile,
4-(2-fluorophenyl)-6-(2-furyl)-2-morpholin-4-ylnicotinonitrile,
tert-butyl *N*-[3-cyano-4-(2-fluorophenyl)-6-(2-furyl)pyridin-2-yl]glycinate,
2-(ethylamino)-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile,
ethyl 4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoate,
2-amino-6-(2-fluorophenyl)-4-(3-furyl)nicotinonitrile,
6-amino-4-(2-fluorophenyl)-2,2'-bipyridine-5-carbonitrile,
2-amino-4-(2-fluorophenyl)-6-thien-2-ylnicotinonitrile,
ethyl 6-amino-5-cyano-4-(2-fluorophenyl)pyridine-2-carboxylate,
2-amino-6-(2-furyl)-4-phenylnicotinonitrile,
ethyl 2-amino-3-cyano-4-(2-furyl)-5,6,7,8-tetrahydroquinoline-6-carboxylate,
2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)-5-methylnicotinonitrile,
2-amino-4-(2-furyl)-6-(4-methoxyphenyl)-5-methylnicotinonitrile,
2-amino-6-(4-fluorophenyl)-4-(2-furyl)-5-methylnicotinonitrile,
2-amino-4-(2-furyl)-5,6-diphenylnicotinonitrile,
2-amino-4-(2-furyl)-5-methyl-6-phenylnicotinonitrile,
2-amino-6-(3,4-dimethylphenyl)-4-(2-furyl)nicotinonitrile,
2-amino-6-(4-fluorophenyl)-4-(2-furyl)nicotinonitrile,

2-amino-4-(3-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile,
6-amino-4-(3-fluorophenyl)-2,4'-bipyridine-5-carbonitrile,
6-amino-4-(2-fluorophenyl)-2,4'-bipyridine-5-carbonitrile,
2-amino-4-butyl-6-methylnicotinonitrile,
2-amino-6-methyl-4-propylnicotinonitrile,
2-amino-4-ethyl-6-methylnicotinonitrile, 2-amino-4,6-dimethylnicotinonitrile,
2-amino-4-[2-(hexyloxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-[2-(beta-D-glucopyranosyloxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
4-[2-(allyloxy)phenyl]-2-amino-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
methyl [2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetate,
2-amino-4-(2-ethoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
ethyl 4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxylate,
2-amino-6-methylnicotinonitrile,
2-amino-6-(4-cyanophenyl)-4-(2-furyl)nicotinonitrile,
2-amino-6-(4-fluorobenzyl)-4-(2-furyl)nicotinonitrile,
2-amino-5-(4-fluorophenyl)-4-(2-furyl)-6-methylnicotinonitrile,
2-amino-4-(2-furyl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-4-(2-methylphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile,
2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile,
2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile,
2-amino-6-(4-methoxyphenyl)-4-(2-methylphenyl)nicotinonitrile,
2-amino-4,6-bis(4-methoxyphenyl)nicotinonitrile,
2-amino-4-(3-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-4-(2-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile,
2-amino-4-(2-furyl)-6-(4-methylphenyl)nicotinonitrile,
2-amino-4-(2-furyl)-6-phenylnicotinonitrile,

6-amino-4-(2-furyl)-2,3'-bipyridine-5-carbonitrile,
2-amino-6-(1,3-benzodioxol-5-yl)-4-(2-furyl)nicotinonitrile,
2-amino-4-isoquinolin-4-yl-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-4-(1-benzothien-3-yl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-6-(4-methoxyphenyl)-4-thien-3-ylnicotinonitrile,
2-amino-4-(3-furyl)-6-(4-methoxyphenyl)nicotinonitrile,
2-amino-6-(4-methoxyphenyl)-4-(1H-pyrrol-2-yl)nicotinonitrile,
2-amino-4-(2-furyl)-6-(1H-pyrrol-2-yl)nicotinonitrile,
2'-amino-6'-(4-methoxyphenyl)-3,4'-bipyridine-3'-carbonitrile,
2-amino-4-[2-(trifluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-furyl)-5H-thiochromeno[4,3-b]pyridine-3-carbonitrile,
2-amino-4-{4-[(2-cyanoethyl)(methyl)amino]phenyl}-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-[2-(2-hydroxyethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(2-methylphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-[4-(dimethylamino)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
2-amino-4-(1H-indol-7-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile,
methyl 4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate,
methyl 2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate,
[2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetic acid,
2-amino-6-phenylnicotinonitrile,
2-amino-6-cyclohexylnicotinonitrile,
2-amino-4-(2-furyl)-6-(1-trityl-1H-pyrazol-4-yl)nicotinonitrile,
2-amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile,

2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile,
2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile
2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid,
2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid,

2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate,
2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile,
[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,
2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,
2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate,
2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

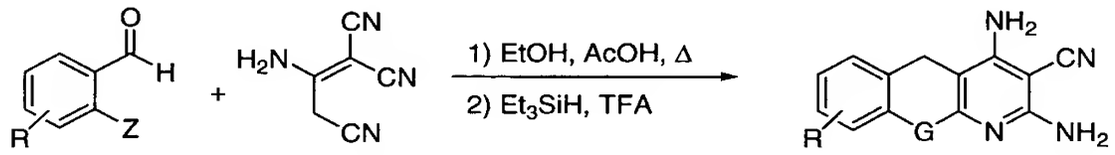
7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,
2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid,
2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and
3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile.

[00060] It should be understood that salts and prodrugs of the aminocyanopyridine compounds that are described herein, as well as isomeric forms, tautomers, racemic mixtures of the compounds, and the like, which have the same or similar activity as the compounds that are described, are to be considered to be included within the description of the compound.

[00061] Aminocyanopyridine MK-2 inhibiting compounds of the type shown in formula II, above, include tricyclic aminocyanopyridine MK-2 inhibiting compounds, such as benzonapthyridines, pyridochromanes, and pyridothiochromanes. A general method for the synthesis of these tricyclic aminocyanopyridines is shown in Scheme 1, below:

Scheme 1:



Z = OH, SH, NR^aY

G = O, S, NR^a

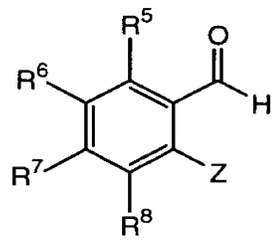
[00062] In this method, a substituted benzaldehyde is reacted with a tricarbonitrile, preferably 2-amino-1-propene-1,1,3-tricarbonitrile. The reaction can be carried out by heating the reactants to reflux in a solution of acetic acid and ethanol. The reaction product can be concentrated *in vacuo* and dissolved in trifluoroacetic acid. Triethylsilane is added and the mixture is stirred. In a preferred method, the mixture is stirred for about 1 hour at 0°C. Dichloromethane is then added and solids are collected. The solids can be collected by filtration, and can be washed with dichloromethane and ether. The solids comprise the desired tricyclic-aminocyanopiyridine MK-2 inhibiting compound of the type including benzonapthyridines, pyridochromanes, and pyridothiochromanes.

[00063] Referring to the reactants and products shown above in Scheme I:

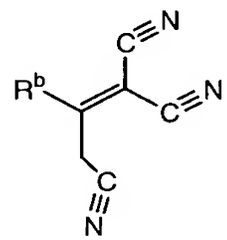
Z can be OH, SH, or NR^aY, where Y is a protecting group for nitrogen. The Y group can be benzyl, allyl, an alkyl carbamate, or a benzyl carbamate. Other nitrogen protecting groups are know to persons having skill in the art of organic synthesis. A perferred protecting group is tert-butylcarbamate. R^a can be an alkyl group, an aryl group, or a heteroaryl group. The benzene ring of the benzaldehyde can be further substituted by one, two, three, or four additional R groups at carbons 3, 4, 5, or 6. Each R can independently be hydrogen; alkyl; aryl; a heteroatom, such as O, N, or S, substituted with hydrogen, C_1-C_6 alkyl, C_1-C_6 branched alkyl, aryl, heteroaryl (wherein the heteroaryl can include, but is not limited to, pyrazolyl, inidizolyl, pyrryl, pyridyl, thiophyl, furyl and pyrimidyl), ester and amido.

[00064] Advantages of this method include that it is a general method that can be used to produce various types of the tricyclic compounds of formula II depending upon the types of reactants used. It is also an easy and straightforward synthesis method that can be carried out in a single vessel.

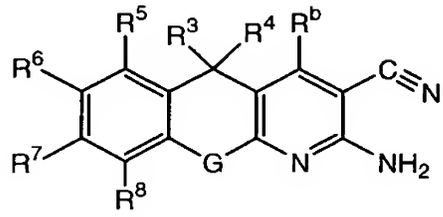
[00065] In an embodiment of this method of synthesis, a tricyclic aminocyanopyridine MK-2 inhibiting compound can be prepared by reacting a substituted benzaldehyde having the structure:



with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



wherein:

Z is selected from the group consisting of -OH, -SH, and -NR^aY;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen. Examples of such nitrogen protecting groups include benzyl, allyl, alkyl carbamates and benzyl carbamates.

G is selected from the group consisting of -O-, -S-, and -NR_x-;

R_x is alkyl;

R^b is selected from the group consisting of furyl and -NH-R^2;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, hydroxy, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, alkylaryl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylamino, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, alkylcarboxyalkoxy,

pyrrolidylethoxy, hydroxyalkoxy, and alkylcarboxy, where R^6 and R^7 are such that they optionally join to form a six membered heterocyclic ring.

[00066] In an embodiment of the general method described above,

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

R^5 is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkylyl, arylalkyl, or alkylaryl;

R^6 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

R^7 is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the R^6 and R^7 groups can join to form a six membered heterocyclic ring; and

R^8 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclylalkyl.

[00067] In a preferred embodiment of this method, the substituted benzaldehyde comprises salicaldehyde and the tricarbonitrile comprises 2-amino-1-propene-1,1,3-tricarbonitrile. It is also preferred that the nitrogen protecting group "Y", comprises tert-butylcarbamate.

[00068] In an embodiment of the present method,

Z is selected from the group consisting of -OH, -SH, and $-NR^aY$;

R_a is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of -O-, -S-, and -NR_x-;

R_x is C_1-C_6 alkyl;

R^b is selected from the group consisting of furyl and -NH-R^2;

R^2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, hydroxy C_1-C_6 alkyl, hydroxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_2-C_6 alkenoxy,

branched or unbranched amino C_1-C_6 alkyl, diamino C_2-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkyl, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_4 alkoxyarylamino, C_1-C_4 alkoxyalkylamino, amino C_1-C_6 alkoxy, di-(C_1-C_4 alkylamino, C_2-C_6 alkoxy, di-(C_1-C_6 alkyl)amino C_1-C_6 alkyl, C_1-C_6 alkylamino C_1-C_6 alkoxy, halo C_1-C_6 alkoxy, dihalo C_1-C_6 alkoxy, trihalo C_1-C_6 alkoxy, cyano C_1-C_6 alkyl, dicyano C_1-C_6 alkyl, cyano C_1-C_6 alkoxy, dicyano C_1-C_6 alkoxy, carbamyl C_1-C_4 alkoxy, heterocyclyl C_1-C_4 alkoxy, heteroaryl C_1-C_4 alkoxy, sulfo, sulfamyl, C_1-C_4 alkylaminosulfonyl, hydroxy C_1-C_4 alkylaminosulfonyl, di-(C_1-C_4 alkyl)aminosulfonyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfinyl,

aryl, aryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkyl, heteroaryl C_1-C_6 alkyl, heterocyclyl C_1-C_6 alkoxy, heteroaryl C_1-C_6 alkoxy, aryl C_1-C_6 alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, halo, amino, and C_1-C_6 alkoxy,

substituted or unsubstituted C_3-C_6 cyclyl, C_3-C_6 heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, amino, and where the C_3-C_6 heterocyclyl ring contains O, S, or N,

branched or unbranched C_1-C_6 alkoxycarbonyl C_1-C_6 alkoxy, and

carboxy, carboxy C_1-C_6 alkoxy, carboxy C_1-C_6 alkyl, hydroxy C_1-C_4 alkoxycarbonyl, C_1-C_4 alkoxycarbonyl.

[00069] And where the terms "alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, haloalkoxy, halo, alkylthio, alkylthioalkyl, heterocyclyl, cyclyl, aryl, heteroaryl, cycloaryl, and oxo" have the same meanings as described above.

[00070] A general method for the synthesis of aminocyanopyridine MK-2 inhibitors that are not tricyclic benzonapthyridines, pyridochromanes, and pyridothiochromanes can be found in Kambe, S. *et al.,* S*ynthesis* *5*:366 - 368 (1980). Further details of the synthesis of aminocyanopyridines are provided in the examples.

[00071] The MK-2 inhibiting activity of an aminocyanopyridine compound can be determined by any one of several methods that are well known to those having skill in the art of enzyme activity testing. One such method is described in detail in the general methods section of the examples. In addition, the efficacy of an aminocyanopyridine MK-2 inhibiting compound in therapeutic applications can be determined by testing for inhibition of TNFα production in cell culture and in animal model assays. In general, it is preferred that the aminocyanopyridine MK-2 inhibiting compounds of the present invention be capable of inhibiting the production and/or the release of TNFα in cell cultures and in animal models.

[00072] In the present method, the aminocyanopyridine MK-2 inhibitor compounds that are described herein can be used as inhibitors of MAPKAP kinase-2. When this inhibition is for a therapeutic purpose, one or more of the present compounds can be administered to a subject that is in need of MK-2 inhibition. As used herein, a "subject in need of MK-2 inhibition" is a subject who has, or who is at risk of contracting a TNFα mediated disease or disorder. TNFα mediated diseases and disorders are described in more detail below.

[00073] In an embodiment of the present method, a subject in need of prevention or treatment of a TNFα mediated disease or disorder is treated with one or more of the present aminocyanopyridine compounds. In one embodiment, the subject is treated with an effective amount of the aminocyanopyridine MK-2 inhibitor compound. The effective amount can be an amount that is sufficient for preventing or treating the TNFα mediated disease or disorder.

[00074] The aminocyanopyridine compound that is used in the subject method can be any aminocyanopyridine compound that is described above.

[00075] In the subject method, the aminocyanopyridine MK-2 inhibitor compound can be used in any amount that is an effective amount. It is preferred, however, that the amount of the aminocyanopyridine compound that is administered is within a range of about 0.1 mg/day per kilogram of the subject to about 150 mg/day/kg. It is more preferred that the amount of the aminocyanopyridine compound is within a range of about 0.1 mg/day/kg to about 20 mg/day/kg. An amount that is within a range of about 0.1 mg/day/kg to about 10 mg/day/kg, is even more preferred.

[00076] When the term "about" is used herein in relation to a dosage amount of the aminocyanopyridine compound, it is to be understood to mean an amount that is within ± 0.05 mg. By way of example, "about 0.1 - 10 mg/day" includes all dosages within 0.05 to 10.05 mg/day.

[00077] In another embodiment of the present invention, a pharmaceutical composition that contains one or more of the aminocyanopyridine MK-2 inhibitors can be administered to a subject for the prevention or treatment of a TNFα mediated disease or disorder. The pharmaceutical composition includes a aminocyanopyridine MK-2 inhibitor of the present invention and a pharmaceutically acceptable carrier.

[00078] In another embodiment, a kit can be produced that is suitable for use in the prevention or treatment of a TNFα mediated disease or disorder. The kit comprises a dosage form comprising an aminocyanopyridine MK-2 inhibitor in an amount which comprises a therapeutically effective amount.

[00079] As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one of ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[00080] The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or inhibition", and both are intended to qualify the amount of an agent for use in therapy which will achieve the goal of improvement in the severity of pain and inflammation

and the frequency of incidence, while avoiding adverse side effects typically associated with alternative therapies.

[00081] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[00082] The frequency of dose will depend upon the half-life of the active components of the composition. If the active molecules have a short half life (*e.g.* from about 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the active molecules have a long half-life (*e.g.* from about 2 to about 15 days) it may only be necessary to give a dosage once per day, per week, or even once every 1 or 2 months. A preferred dosage rate is to administer the dosage amounts described above to a subject once per day.

[00083] For the purposes of calculating and expressing a dosage rate, all dosages that are expressed herein are calculated on an average amount-per-day basis irrespective of the dosage rate. For example, one 100 mg dosage of an aminocyanopyridine MK-2 inhibitor taken once every two days would be expressed as a dosage rate of 50 mg/day. Similarly, the dosage rate of an ingredient where 50 mg is taken twice per day would be expressed as a dosage rate of 100 mg/day.

[00084] For purposes of calculation of dosage amounts, the weight of a normal adult human will be assumed to be 70 kg.

[00085] When the aminocyanopyridine MK-2 inhibitor is supplied along with a pharmaceutically acceptable carrier, the pharmaceutical compositions that are described above can be formed. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the

compound is not canceled or inhibited to such an extent that treatment is ineffective.

[00086] The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

[00087] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[00088] Also included in the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of the aminocyanopyridine MK-2 inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic),

methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

[00089] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trifluoroacetate, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

[00090] The method of the present invention is useful for, but not limited to, the prevention and treatment of diseases and disorders that are mediated by TNFα. For example, the aminocyanopyridine MK-2 inhibitors of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such aminocyanopyridine MK-2 inhibitor compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis; eczema, burns and dermatitis.

[00091] The aminocyanopyridine MK-2 inhibitor compounds that are useful in the method of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as

colorectal cancer. Such aminocyanopyridine MK-2 inhibiting compounds would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

[00092] The aminocyanopyridine MK-2 inhibitors would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. These compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease.

[00093] As used herein, the terms "TNFα mediated disease or disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

[00094] The terms "treating" or "to treat" mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described herein. Besides being useful for human treatment, the subject compounds are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

[00095] The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of or treatment

of any one of the TNFα mediated diseases or disorders. The subject is typically a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc., Preferably, the mammal is a human.

[00096] For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of a TNFα mediated disease or disorder. The subject may be a human subject who is at risk of obtaining a TNFα mediated disease or disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

[00097] The subject pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[00098] In particular, the pharmaceutical compositions of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate,

sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[00099] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000100] Aqueous suspensions can be produced that contain the aminocyanopyridine MK-2 inhibitors in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000101] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or

more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000102] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000103] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000104] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000105] Syrups and elixirs containing the novel compounds may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000106] The subject compositions can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are

water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono-, or di-, glycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000107] The subject compositions can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

[000108] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

[000109] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[000110] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

[000111] The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are given on a weight basis unless otherwise indicated.

GENERAL INFORMATION FOR PREPARATION METHODS:

[000112] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

[000113] NMR analysis:

[000114] Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer, a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer, a PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), or a Waters ZQ mass spectrometer (ESI).

[000115] Determination of MK-2 IC_{50}:

[000116] Recombinant MAPKAPK2 was phosphorylated at a concentration of 42-78 μM by incubation with 0.23 μM of active p38α in 50 mM HEPES, 0.1 mM EDTA, 10 mM magnesium acetate, and 0.25 mM ATP, pH 7.5 for one hour at 30°C.

[000117] The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay method. The reaction was carried out in 50 mM β-glycerolphosphate, 0.04 % BSA, 10 mM magnesium acetate, 2% DMSO and 0.8 mM dithiotheritol, pH 7.5 in the presence of the HSP-peptide with 0.2 μCi [γ^{33}P]ATP and 0.03mM ATP. The reaction was initiated by the addition of 15 nM MAPKAPK2 and was allowed to incubate at 30ºC for 30 min. The reaction was terminated and [γ^{33}P]ATP was removed from solution by the addition of 150 μl of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3.0. A 50 μl aliquot of head volume was removed from the quenched reaction mixture and added to a 96-well plate, 150 μl of Microscint-40 (Packard)

was added and the amount of phosphorylated-peptide was determined. Allow the Microscint to sit in the plates for 60 minutes prior to counting.

[000118] Compounds are evaluated as potential inhibitors of the MK2 kinase by measuring their effects on MK2 phosphorylation of the peptide substrate. Compounds may be screened initially at two concentrations prior to determination of IC_{50} values. Screening results are expressed as percent inhibition at the concentrations of compound tested. For IC_{50} value determinations, compounds are tested at six concentrations in ten-fold serial dilutions with each concentration tested in triplicate. Results are expressed as IC_{50} values in micromolar. The assay is performed at a final concentration of 2% DMSO.

[000119] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide IC_{50} values for MK-2 inhibition of below 200 μM. One method that can be used for determining the MK-2 inhibition IC_{50} value is that described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing MK-2 inhibition IC_{50} values of below 100 μM, yet more preferred of below 50 μM, even more preferred of below 20 μM, yet more preferred of below 10 μM, and even more preferred of below 1μM.

[000120] U937 Cell TNFα release assay

[000121] The human monocyte-like cell line, U937 (ATCC #CRL-1593.2), is cultured in RPMI1640 media with 10% heat-inactivated fetal calf serum (GIBCO), glutamine and pen/strep at 37°C and 5% CO_2. Differentiation of U937 to monocytic/macrophage-like cells is induced by the addition of phorbol12-myristate 13-acetate (Sigma) at final concentration of 20 ng/ml to a culture of U937 cells at ~0.5 million cells/ml and incubated for 24 hrs. The cells are centrifuged, washed with PBS and resuspended in fresh media without PMA and incubated for 24 hrs. Cells adherent to the culture flask are harvested by scraping, centrifugation, and resuspended in fresh media to 2 million cells/ml, and 0.2 ml is aliquoted to each of 96 wells in flat-bottom plate. Cells are then incubated for an additional 24 hrs to allow

for recovery. The media is removed from the cells, and 0.1 ml of fresh media is added per well. 0.05 ml of serially diluted compound or control vehicle (Media with DMSO) is added to the cells. The final DMSO concentration does not exceed 1%. After 1hr incubation, 0.05 ml of 400ng/ml LPS (E Coli serotype 0111:B4, Sigma) in media is added for final concentration of 100 ng/ml. Cells are incubated at 37°C for 4 hrs. After 4hrs incubation, supernatants are harvest and assayed by ELISA for the presence of TNFα.

[000122] U937 cell TNFα ELISA

[000123] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with purified mouse monoclonal IgG1 anti-human TNFα antibody (R&D Systems #MAB610; 1.25 ug/ml in sodium bicarbonate pH 8.0, 0.1 ml/well) and incubated at 4°C. Coating solution was aspirated the following day and wells were blocked with 1 mg/ml gelatin in PBS (plus 1x thimerasol) for 2 days at 4°C. Prior to using, wells were washed 3x with wash buffer (PBS with 0.05% Tween). Cultured media samples were diluted in EIA buffer (5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS), added to wells (0.1 ml/well) in triplicate and allowed to incubate for 1.5 hr at 37°C in a humidified chamber. Plates were again washed and 0.1 ml/well of a mixture of rabbit anti-human TNFα polyclonal antibodies in EIA buffer (1:400 dilution of Sigma #T8300, and 1:400 dilution of Calbiochem #654250) was added for 1 hr at 37°C. Plates were washed as before and peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody (Jackson ImmunoResearch #111-035-144, 1 ug/ml in EIA buffer, 0.1 ml/well) was added for 45 min. After final washing, plates were developed with peroxidase-ABTS solution (Kirkegaard/Perry #50-66-01, 0.1 ml/well). Enzymatic conversion of ABTS to colored product was measured after 5-30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices) at 405 nm. TNF levels were quantitated from a recombinant human TNFα (R&D Systems #210-TA-010) standard curve using a quadratic parameter fit generated by

SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. IC_{50} values for compounds were generated using BioAssay Solver.

[000124] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide TNFα release IC_{50} values of below 200 μM in an *in vitro* cell assay. One method that can be used for determining TNFα release IC_{50} in an *in vitro* cell assay is that described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing TNFα release IC_{50} values of below 50 μM, yet more preferred of below 10, and even more preferred of below 1.0 μM.

[000125] Lipopolysaccharide (LPS)-Induced TNFα Production.

[000126] Adult male 225-250 gram Lewis rats (Harlan Sprague-Dawley) were used. Rats were fasted 18 hr prior to oral dosing, and allowed free access to water throughout the experiment. Each treatment group consisted of 5 animals.

[000127] Compounds were prepared as a suspension in a vehicle consisting of 0.5% methylcellulose, 0.025% Tween-20 in PBS. Compounds or vehicle were orally administered in a volume of 1 ml using an 18 gauge gavage needle. LPS (E. coli serotype 0111:B4, Lot #39H4103, Cat. # L-2630, Sigma) was administered 1-4 hr later by injection into the penile vein at a dose of 1 mg/kg in 0.5 ml sterile saline. Blood was collected in serum separator tubes via cardiac puncture 1.5 hr after LPS injection, a time point corresponding to maximal TNFα production. After clotting, serum was withdrawn and stored at -20°C until assay by ELISA (described below).

[000128] Rat LPS TNFα ELISA

[000129] ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with 0.1 ml per well of an Protein G purified fraction of a 2.5 ug/ml of hamster anti-mouse/rat TNFα monoclonal antibody TN19.12 (2.5 ug/ml in PBS, 0.1 ml/well). The hybridoma cell line was kindly provided by Dr. Robert Schreiber, Washington University. Wells were blocked the

following day with 1 mg/ml gelatin in PBS. Serum samples were diluted in a buffer consisting of 5 mg/ml bovine γ-globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS, and 0.1 ml of diluted serum was added wells in duplicate and allowed to incubate for 2 hr at 37°C. Plates were washed with PBS-Tween, and 0.1 ml per well of a 1:300 dilution of rabbit anti-mouse/rat TNFα antibody (BioSource International, Cat. #AMC3012) was added for 1.5 hr at 37°C. Plates were washed, and a 1:1000 fold dilution of peroxidase-conjugated donkey anti-rabbit IgG antibody (Jackson ImmunoResearch, Cat. #711-035-152) was added for 45 min. After washing, plates were developed with 0.1 ml of ABTS-peroxide solution (Kirkegaard/Perry, Cat. #50-66-01). Enzymatic conversion of ABTS to colored product was measured after ~30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices Corp.) at 405 nm. TNF levels in serum were quantitated from a recombinant rat TNFα (BioSource International, Cat. #PRC3014.) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. Results are expressed in percent inhibition of the production of TNFα as compared to blood collected from control animals dosed only with vehicle.

[000130] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention are capable of providing some degree of inhibition of TNFα in animals. That is, the degree of inhibition of TNFα in animals is over 0%. One method for determining the degree of inhibition of TNFα is the rat LPS assay that is described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing rat LPS TNFα inhibition values of at least about 25%, even more preferred of above 50%, yet more preferred of above 70%, and even more preferred of above 80%.

[000131] Synthesis of aminocyanopyridine compounds:

[000132] A general method for the synthesis of aminocyanopyridines described in Examples 1 - 213 can be found in Kambe, S. *et al.,* "A simple

method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis 5*:366 - 368 (1980). Further details of the synthesis of aminocyanopyridines of the present invention are provided below.

EXAMPLE 1

[000133] This example illustrates the production of 2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile trifluoroacetate.

[000134] 2-Fluorobenzaledhyde (5 mmol, 1.0 equiv., 530μL), 3,4-dihydroxyacetophenone (5 mmol, 1.0 equiv., 760mg) malononitrile (5 mmol, 1.0 equiv., 290μL) and ammonium acetate (7.5 mmol, 1.5 equiv., 578mg) were combined in dichloroethane (10 mL) and heated to reflux for 4 hours. Dichloroethane was evaporated and the residue was purified by reverse phase chromatography. The product was isolated as an orange solid (145mg, 8% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.70 (d, 1H), 7.59-7.53 (m, 3H), 7.37 (d, 1H), 7.32 (t, 1H), 7.18 (s, 1H), 6.90 (d, 1H), 6.34 (bs, 1H) 3.21 (bs, 4H): m/z 322 (M+H).

EXAMPLE 2

[000135] This example illustrates the production of 2-amino-4-(2-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate.

[000136] 2-Fluorobenzaledhyde (2 mmol, 1.0 equiv., 210μL), and malononitrile (2 mmol, 1.0 equiv., 126μL) were combined in toluene (3 mL) and heated to 50°C for 0.5 hours. 2-acetyl furan (2 mmol, 1.0 equiv., 146mg) and ammonium acetate (3 mmol, 1.5 equiv., 230mg) were added and the reaction stirred at 55°C overnight. Amberlyst resin (1g) was added and the reaction was diluted with dichloromethane. After shaking overnight, the resin was isolated by filtration and washed with dichloromethane and methanol. The resin was treated with 2M ammonia in methanol. After shaking overnight, the resin was removed by filtration and the filtrate concentrated under a stream of nitrogen. The residue was

purified by reverse phase chromatography and the product was isolated as a brown solid (50mg, 9%). ^{1}H NMR (300 MHz, DMSO) δ 7.78 (s, 1H), 7.65-7.75 (m, 2H), 7.43-7.35 (m, 2H), 7.22 (d, 1H), 7.14 (s, 1H), 6.67 (s, 1H) 6.48 (bs, 2H): m/z 280 (M+H).

EXAMPLE 3

[000137] This example illustrates the production of 2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000138] Step 1: Production of 2-(1H-imidazol-5-ylmethylene)malononitrile.

[000139] 1H-imidazole-5-carbaldehyde (20 mmol, 1.0 equiv., 1.92g), and malononitrile (20 mmol, 1.0 equiv., 1.26mL) were combined in trimethylorthoformate (30 mL) and triethylamine (7mL). After stirring at room temperature overnight, the solvents were evaporated and the residue partitioned between 1M hydrochloric acid (HCl) and dichloromethane. The aqueous layer was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate ($MgSO_4$), filtered and evaporated to give the product as a yellow solid (2.58g, 90%). ^{1}H NMR (400 MHz, Acetone) δ 12.11 (bs, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H): m/z 143 (M-H).

[000140] Step 2: Production of 2-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-inidazol-5-yl)methylene)malononitrile;

[000141] 2-(1H-imidazol-5-ylmethylene)malononitrile, (2 mmol, 1.0 equiv., 288mg), prepared as described in Step 1, was added to a cool (0°C) suspension of sodium hydride (60% in mineral oil, 1.1 equiv., 50 mg) in tetrahydrofuran (THF) (15 mL). After 20 minutes, [2-(chloromethoxy)ethyl](trimethyl)silane (2.2 mmol, 1.1 equiv., 390μL) was added and the solution warmed to room temperature overnight. The reaction was treated with water (5mL) and concentrated the residue was extracted with ethyl acetate (25 mL) and the layers separated. Dried organic extract with $MgSO_4$, filtered and evaporated to give a brown solid. The product was purified by silica gel chromatography. The product was

isolated as a yellow solid, (277mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.98 (s, 1H), 7.76 (s, 1H), 5.34 (s, 2H) 3.52 (dd, 2H), 0.92 (dd, 2H), -0.01 (s, 9H): m/z 275 (M+H).

[000142] Step 3: Production of 2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000143] 2-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-inidazol-5-yl)methylene)malononitrile (0.8 mmol, 1.0 equiv., 220mg), prepared as described in Step 2, above, 4-hydroxyacetophenone (0.8mmol, 1.0 equiv., 109mg) and ammonium acetate (1.2 mmol, 1.5 equiv., 95mg) were combined in toluene (3 mL) and benzene (1mL) heated to 80°C overnight. After cooling, Amberlyst resin (1g) was added and the mixture heated to 50°C overnight. The resin was isolated by filtration and washed with dichloromethane and methanol. The resin was treated with 2M ammonia in methanol. The resin was removed by filtration and the filtrate concentrated under a stream of nitrogen. The residue was purified by reverse phase chromatography and the product was isolated as a solid (25mg, 11%). ^{1}H NMR (300 MHz, Acetone) δ 8.59 (s, 1H), 8.32 (s, 1H), 8.12 (d, 2H), 7.87 (s, 1H), 6.97 (d, 2H), 6.73 (bs, 1H): m/z 278 (M+H).

EXAMPLE 4

[000144] This illustrates the production of 2-amino-6-(3-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000145] 2-amino-6-(3-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate was prepared in the same manner as 2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate, as described in Example 3. The amount produced was 25mg, at a yield of 11%. ^{1}H NMR (300 MHz, Acetone) δ 8.51 (s, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.76 (t, 1H) 7.66 (d, 2H), 7.34 (t, 1H), 6.98 (dd, 1H), 6.59 (bs, 1H): m/z 278 (M+H). TNFα release assay IC50: 7.0 μM; Rat LPS assay: 41% inhibition of TNFα production at 20 mpk (IG).

EXAMPLE 5

[000146] This illustrates the production of 2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000147] 2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate was prepared in the same manner as 2-amino-6-(4-hydroxyphenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate, as described in Example 3. The amount produced was 20mg, at a yield of 10%. ^{1}H NMR (300 MHz, Acetone) δ 8.40 (s, 1H), 8.29 (s, 1H), 7.81 (m, 2H), 7.27 (d, 1H), 6.70-6.68 (m, 2H): m/z 252 (M+H).

EXAMPLE 6

[000148] This illustrates the production of intermediate 2-[1-(1-methyl-1H-imidazol-4-yl)ethylidene]malononitrile.

[000149] 2-(1H-imidazol-5-ylmethylene)malononitrile (3.92 mmol, 1.0 equiv., 565mg), prepared as described in Step 1 of Example 3, was dissolved in THF and cooled to 0°C. Sodium hydride (60% in mineral oil, 1.1 equiv., 103 mg) as added followed by dimethylsulfate (4.31 mmol, 1.1 equiv., 410µL). The solution warmed to room temperature overnight. The reaction was treated with water and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$, filtered and evaporated to give a solid. The product was isolated as a white solid, (500mg, 80%). ^{1}H NMR (300 MHz, Acetone) 8.01 (s, 2H), 7.85 (s, 1H), 3.92: m/z 159 (M+H). The material can be used as an intermediate as shown next, for the preparation of an aminocyanopyridine compound.

EXAMPLE 7

[000150] This illustrates the production of 2-amino-6-(2-furyl)-4-(1-methyl-1H-imidazol-4-yl)nicotinonitrile bis(trifluoroacetate).

[000151] 2-[1-(1-methyl-1H-imidazol-4-yl)ethylidene]malononitrile (1.0 mmol, 1.0 equiv., 158mg), 2-acetylfuran (1.0 mmol, 1.0 equiv., 100µL) and ammonium acetate (1.5 mmol, 1.5 equiv., 115mg) were combined in toluene (2 mL) and benzene (1mL) heated to 70°C overnight. After cooling, Amberlyst resin (1g) was added and the mixture shaken overnight. The resin was isolated by filtration and washed with dichloromethane and methanol. The resin was treated with 2M ammonia in methanol. The resin was removed by filtration and the filtrate concentrated under a stream of nitrogen. The residue was purified by

reverse phase chromatography and the product was isolated as a solid (35mg, 13%). ^{1}H NMR (400 MHz, Acetone) δ 8.08 (s, 1H), 7.91 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.19 (d, 1H), 6.64 (d, 1H) 6.46 (bs, 2H), 3.94 (s, 3H): m/z 266 (M+H).

EXAMPLE 8

[000152] This illustrates the production of 2-amino-4-(1-methyl-1H-imidazol-4-yl)-6-phenylnicotinonitrile bis(trifluoroacetate).

[000153] 2-amino-4-(1-methyl-1H-imidazol-4-yl)-6-phenylnicotinonitrile bis(trifluoroacetate) was prepared in the same manner as 2-amino-6-(2-furyl)-4-(1-methyl-1H-imidazol-4-yl)nicotinonitrile bis(trifluoroacetate), as described in Example 7, with the production of 40mg of solid material and with a yield of 13%. ^{1}H NMR (400 MHz, Acetone) δ 8.15 (bs, 4H), 7.91 (s, 1H), 7.48 (s, 3H), 4.00 (s, 3H): m/z 276 (M+H).

EXAMPLES 9 - 58

[000154] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000155] The compounds listed in the table below were prepared by the methods described in Kambe, S. *et al.*, "A simple method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis* 5:366 - 368 (1980). NMR analysis was carried out for each compound and selected data is presented for each compound as shown in the table.

Ex. No.	Compound name	m/z (M+H)
9	4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoic acid hydrochloride	306
10	2-amino-6-(3,4-dihydroxyphenyl)-4-(2-fluorophenyl)nicotinonitrile	322
11	2-amino-4-(1H-imidazol-5-yl)-6-phenylnicotinonitrile trifluoroacetate	262
12	2-amino-4-(1H-imidazol-5-yl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	292

Ex. No.	Compound name	m/z (M+H)
13	8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	339
14	2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	296
15	4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzenesulfonamide trifluoroacetate	341
16	2-amino-4-(2-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	306
17	2-amino-4-(2-bromophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	340
18	2-amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	306
19	2-amino-6-(4-chlorophenyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate	296
20	2-amino-4-(1H-imidazol-5-yl)-6-[4-(methylsulfonyl)phenyl]nicotinonitrile trifluoroacetate	340
21	ethyl 4-[6-amino-5-cyano-4-(1H-imidazol-5-yl)pyridin-2-yl]benzoate trifluoroacetate	334
22	2-amino-4-cyclopropyl-6-methylnicotinonitrile trifluoroacetate	174
23	2-amino-6-(2-furyl)-4-(4-phenoxyphenyl)nicotinonitrile trifluoroacetate	354
24	4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid trifluoroacetate	306
25	4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]benzoic acid trifluoroacetate	306
26	2-amino-4-(2-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	320
27	2-amino-4-(3-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	306
28	2-amino-4-(3-fluorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	320
29	2-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]phenylboronic acid trifluoroacetate	306
30	2-amino-6-(2-furyl)-4-[4-(trifluoromethyl)phenyl]nicotinonitrile trifluoroacetate	330

Ex. No.	Compound name	m/z (M+H)
31	2-amino-4-(4-bromophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	340
32	2-amino-4-[2-fluoro-4-(trifluoromethyl)phenyl]-6-(2-furyl)nicotinonitrile trifluoroacetate	348
33	2-amino-4-(3-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	280
34	2-amino-4-(4-fluorophenyl)-6-(2-furyl)nicotinonitrile trifluoroacetate	280
35	2-amino-6-(4-methoxyphenyl)-4-thien-3-ylnicotinonitrile trifluoroacetate	308
36	2-amino-4-(3-furyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	292
37	2-amino-6-(4-methoxyphenyl)-4-(1H-pyrrol-2-yl)nicotinonitrile trifluoroacetate	291
38	2-amino-6-(4-methoxyphenyl)-4-thien-2-ylnicotinonitrile trifluoroacetate	308
39	2-amino-4-(3-chlorophenyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	336
40	2-amino-4-(2-chlorophenyl)-6-(4-methoxyphenyl) nicotinonitrile trifluoroacetate	336
41	2'-amino-6'-(4-methoxyphenyl)-3,4'-bipyridine-3'-carbonitrile trifluoroacetate	303
42	2-amino-4-isoquinolin-4-yl-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	353
43	2-amino-4-(1-benzothien-3-yl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	358
44	2-amino-4-(2-furyl)-6-(4-methoxyphenyl)nicotinonitrile trifluoroacetate	292
45	2-amino-4-(2-methylphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile trifluoroacetate	263
46	2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile trifluoroacetate	280
47	2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile	250
48	2-amino-6-(4-methoxyphenyl)-4-(2-methylphenyl)nicotinonitrile trifluoroacetate	316

Ex. No.	Compound name	m/z (M+H)
49	2-amino-4,6-bis(4-methoxyphenyl)nicotinonitrile trifluoroacetate	332
50	2-amino-6-(4-methoxyphenyl)-4-phenylnicotinonitrile trifluoroacetate	302
51	2-amino-4-butyl-6-methylnicotinonitrile trifluoroacetate	190
52	2-amino-6-methyl-4-propylnicotinonitrile trifluoroacetate	176
53	2-amino-4-ethyl-6-methylnicotinonitrile trifluoroacetate	162
54	2-amino-4,6-dimethylnicotinonitrile trifluoroacetate	148
55	6-amino-4-(3-fluorophenyl)-2,4'-bipyridine-5-carbonitrile trifluoroacetate	291
56	2-amino-4-(3-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	306
57	2-amino-4-(3-fluorophenyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	306
58	6-amino-4-(2-fluorophenyl)-2,4'-bipyridine-5-carbonitrile trifluoroacetate	291

EXAMPLE 59

[000156] This illustrates the production of 4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxamide.

[000157] A mixture of malononitrile (20mmol, 1.32g), ethyl 4-formylpyrrole-2-carboxylate (20mmol, 3.34g), 2-acetylfuran (20 mmol, 2.2g) and ammonium acetate (30 mmol, 2.32g) in toluene (25mL) was heated under reflux for 24 hours with azeotropic removal of water. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure to dryness and the residue was stirred with ethanol (15ml) for 4 hours. The resultant precipitate was collected by filtration, washed with aqueous ethanol and air-dried. Recrystallization of the solid from tetrahydrofuran gave a yellow-brown powder (2.25 g, 35% yield): ^{1}H NMR (400 MHZ, DMSO) δ 12.42 (s, 1H), 7.836 (s, 1H), 7.776 (d, 1H), 7.404 (d, 1H), 7.220 (s, 1H), 7.195 (d, 1H), 6.797 (s, 2H), 6.642(dd, 1H), 4.257 (q, 2H), 1.277 (t, 3H).

[000158] To a suspension of the above solid (5mmol, 1.6g) in ethanol (50mL) was added aqueous sodium hydroxide(10% wt/volume, 15mmol, 6ml) and the mixture was warmed at 60°C for 5 hours. The resultant solution was kept at room temperature overnight and then evaporated under reduced pressure. The residue was dissolved in warm water (50 ml), then acidified with 5% HCl solution to pH = 3. The resultant precipitate was collected by filtration, washed with water and dried under vacuum to give a greyish powder. To a solution of the above solid (1mmol, 0.294g) in dry dimethylformamide (12ml) was added 1,1'-carbonyldiimidazole (1.2mmol, 0.195g) in one portion and the mixture was stirred at 50°C for 2 hours. After cooling to room temperature, ammonia was bubbled into the reaction mixture for 30 minutes and then kept at room temperature for 48 hours. The mixture was evaporated *in vacuo* to dryness and the residue was stirred with water (10ml). The resultant precipitate was collected by filtration, washed successively with water and ether and recrystallized from methanol to give the product as a gray powder (0.182g, 62% yield): ^{1}H NMR (400 MHz, DMSO) δ 7.812 (s, 1H), 7.459 (d, 1H), 7.147 (s, 1H), 7.128 (d, 1H), 6.915 (d, 1H), 6.620 (m, 3H); m/z 294 (M+H).

EXAMPLES 60 - 75

[000159] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000160] The compounds listed in the table below were prepared by the methods described in Kambe, S. *et al.*, "A simple method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis* 5:366 - 368 (1980). NMR analysis was carried out for each compound and selected data is presented for each compound as shown in the table.

[000161]

Ex. No.	Compound name	m/z (M+H)
60	4,6-diamino-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile or 6N009	245
61	4,6-diamino-2-(chloromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	225
62	4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxylate	295
63	4,6-diamino-2-[(4-methoxyphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	313
64	4,6-diamino-2-(hydroxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	207
65	2,4-diamino-6-[(4-methoxyphenyl)thio]nicotinonitrile	273
66	4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	283
67	4,6-diamino-2-[(2-methylphenoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	297
68	2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	266
69	2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	280
70	2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	266
71	2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	252
72	2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	272

Ex. No.	Compound name	m/z (M+H)
73	2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	316, 318
74	2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	238
75	ethyl 4-[2-amino-3-cyano-6-(2-furyl)pyridin-4-yl]-1H-pyrrole-2-carboxylate	323

EXAMPLE 76

[000162] This illustrates the production of 2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000163] Step 1: Production of 2-amino-6-(2-furyl)-4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-4-yl)nicotinonitrile.

[000164] To a solution of 2-Acetylfuran (0.96 g, 8.71 mmol) and 2-[(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-5-yl)methylene]malononitrile (2.0 g, 7.3 mmol) in benzene (15 mL) at room temperature was added ammonium acetate (1.08 g, 14.1 mmol). After heating to reflux for 10 hrs the reaction was cooled to room temperature and diluted with ethyl acetate and water. The layers were separated and the organic layer washed with brine and dried sodium sulfate (Na_2SO_4). The solvent was removed to give a solid, which after chromatography (silica, 30% ethyl acetate/hexane) gave the desired product (0.78 g, 38%). ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.14 (s, 1H), 8.02 (s, 1H), 7.88 (s, 1H), 7.57 (s, 1H), 7.10 (d, J = 3.3 Hz, 1H), 6.81 (bm, 2H), 6.67 (m, 1H), 5.44 (s, 2H), 3.53 (t, J = 7.5 Hz, 2H), 0.86 (t, J = 7.5 Hz, 2H), 0.05 (s, 9H): m/z 382 (M+H).

[000165] Step 2: Production of 2-amino-6-(2-furyl)-4-(1H-imidazol-5-yl)nicotinonitrile trifluoroacetate.

[000166] To a round bottom flask containing 2-amino-6-(2-furyl)-4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazol-4-yl)nicotinonitrile (0.42 g, 1.10 mmol), prepared as described in Step 1, above, was added 0.5 M HCl/ethyl alcohol (EtOH) (15 mL) at room temperature. The reaction was heated to reflux for 5 hrs and then allowed to cool. A precipitate formed

upon cooling and was filtered. The solid was collected and purified by reverse phase high pressure liquid chromatography (RP-HPLC) (H_2O:CH_3CN+j0.05%TFA) to give the desired product after lypholization (0.22 g, 61% yield). ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.46 (bs, 1H), 8.11 (s, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.48 (s, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.69 (dd, J = 1.8, 3.3 Hz, 1H), 3.7 (bm, 3H): m/z 252 (M+H).

EXAMPLE 77

[000167] This illustrates the production of ethyl 4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoate.

[000168] To a solution of ethyl 4-acetylbenzoate (1.12 g, 5.83 mmol) and 2-(2-fluorobenzylidene)malononitrile (1.0 g, 5.81 mmol) in benzene at room temperature was added ammonium acetate (0.67 g, 8.69 mmol). The reaction mixture was heated to reflux for 4 hrs and then allowed to cool to room temperature. The reaction mixture was poured into ethanol and the precipitate filtered to give a light yellow solid (0.30 g, 14% yield). ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.24 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.1 Hz, 2H), 7.60-7.58 (bm, 2H), 7.40-7.34 (bm, 4H), 7.17 (bs, 1 H), 4.34 (q, 2H), 1.32 (t, 3H): m/z 362 (M+H).

EXAMPLE 78

[000169] This illustrates the production of 4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoic acid trifluoroacetate.

[000170] To a solution of ethyl-4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoate (0.20 g, 0.55 mmol) in THF/H_2O (9:1) was added aqueous lithium hydroxide ($LiOH{\cdot}H_2O$) at room temperature. The reaction was heated to reflux for 4 hrs and the solvent removed in vacuo to give a solid, which was purified by RP-HPLC to give the desired product (0.091 g, 50% yield). ^{1}H NMR (300 MHz, d^6-DMSO) δ 8.27(d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 7.66-7.62 (bm, 2H), 7.52-7.40 (bm, 3H), 7.21 (bs, 1H), 4.81 (bs, 2H): m/z 334 (M+H).

EXAMPLE 79

[000171] This illustrates the production of 2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile trifluoroacetate.

[000172] Step 1: Production of 1-(1H-pyrazol-5-yl)-1-ethanone.

[000173] To a solution of KOH (18 g in 50 mL of water) was added diethyl ether. The solution was cooled to 0 °C and 1-Methyl-3-1-nitrosoguanidine (MNNG), (4.0 g) was added slowly to generate diazomethane (CH_2N_2). After this addition was complete the CH_2N_2 in diethyl ether was transferred to a solution of 3-Butyn-2-one (4.0 g, 0.058 mol) in ether via pipet. The reaction was stirred at room temperature for 4 hrs and the solvent removed in vacuo to give an oil, which on high vacuum turned to a solid (1.71 g, 26% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 2.60 (s, 3H).

[000174] Step 2: Production of 2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile trifluoroacetate.

[000175] To a solution of 1-(1H-pyrazol-5-yl)-1-ethanone (0.64 g, 5.80 mmol), prepared as described above in Step 1, furaldehyde (0.48 mL, 5.80 mmol), and malononitrile (0.38 g, 5.80 mmol) in benzene (15 mL) at room temperature was added ammonium acetate (1.11 g, 14.5 mmol). The reaction was heated to reflux for 10 hrs and then allowed to cool to room temperature. The mixture was diluted with water and ethyl acetate. The layers were separated and the organic layer washed with brine and dried, using Na_2SO_4. The solvent was removed to give a brown solid, which after RP-HPLC (H_2O:CH_3CN+0.05%TFA) gave the desired product (185 mg, 12% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.0 (d, J = 1.2 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.61 (s, 1H), 7.46 (d, J = 3.6 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.78-6.76 (m, 1H); m/z 252 (M+H).

EXAMPLES 80 - 91

[000176] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000177] The compounds listed in the table below were prepared by the methods described in Kambe, S. *et al.*, "A simple method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis 5*:366 - 368 (1980). NMR analysis was

carried out for each compound and selected data is presented for each compound as shown in the table.

Ex. No.	Compound name	m/z (M+H)
80	2-amino-4-(1H-imidazol-4-yl)-6-phenylnicotinonitrile trifluoroacetate hydrate	262
81	2-amino-4-(2-fluorophenyl)-6-(1H-pyrrol-2-yl)nicotinonitrile trifluoroacetate hydrate	279
82	2-amino-6-(3-chlorophenyl)-4-(1H-imidazol-4-yl)nicotinonitrile trifluoroacetate hydrate	296
83	2-amino-4-(2-fluorophenyl)-6-phenylnicotinonitrile	290
84	ethyl 4-[6-amino-5-cyano-4-(2-fluorophenyl)pyridin-2-yl]benzoate	334
85	2-amino-6-(2-fluorophenyl)-4-(3-furyl)nicotinonitrile trifluoroacetate	280
86	2-amino-4-(2-fluorophenyl)-6-thien-2-ylnicotinonitrile hydrate	296
87	6-amino-4-(2-fluorophenyl)-2,2'-bipyridine-5-carbonitrile trifluoroacetate	291
88	2-amino-4-(2-furyl)-6-(1H-pyrazol-4-yl)nicotinonitrile bis(trifluoroacetate)	252
89	2-amino-4-(2-furyl)-6-(1-trityl-1H-pyrazol-4-yl)nicotinonitrile	494
90	2-amino-4-(2-fluorophenyl)-6-tetrahydrofuran-2-ylnicotinonitrile	284
91	ethyl 6-amino-5-cyano-4-(2-fluorophenyl)pyridine-2-carboxylate	286

EXAMPLE 92

[000178] This illustrates the production of 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate.

[000179] A glass vial was charged with 6-hydroxy-2-tetralone (0.49 g, 3 mmol), malononitrile, (0. g, 3 mmol), ammonium acetate (0. g, 6 mmol), furaldehyde (0. g, 3 mmol) and a magnetic stirring bar. Benzene (6 mL) was added to the vial, which was capped and heated to 80 degrees Celsius for 18 hours. The vial was then cooled to room temperature, and a 1:2 mixture of methanol and dichloromethane (15 mL) was added followed by 8 g of Amberlyst resin. The mixture was agitated for 24 h, then the resin was filtered and washed with dichloromethane (3X15 mL). A 2 M solution of ammonia in methanol (15 mL) was added to the resin, and the mixture was agitated overnight at room temperature. The resin was filtered and the filtrate collected in a tared flask. The resin was washed sequentially with a 1:1 mixture of methanol and dichloromethane (2X15 mL), 2 M ammonia in methanol (2X15 mL), and a 1:1 mixture of methanol and dichloromethane (2X15 mL). The combined filtrates were concentrated in vacuo, and the residue was purified by reverse phase chromatography. The product was isolated as a tan solid (10.4 mg, 1% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.70 (m, 4H), 6.63 (d, 1H), 6.70 (dd, 1H), 6.73 (d, 1H), 6.87 (d, 1H), 7.91 (d, 1H), 7.96 (d, 1H); m/z 304 (M+H); HRMS (M+H) calculated for $C_{18}H_{14}N_3O_2$: 304.1086, found 304.1086.

EXAMPLE 93

[000180] This illustrates the production of 2-amino-4-(2-furyl)-6,8-dihydro-5H-pyrrolo[3,4-h]quinoline-3-carbonitrile trifluoroacetate.

[000181] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (171.9 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.60 (m, 2H), 2.74 (m, 2H), 6.65 (s, 1H), 6.73 (dd, 1H), 6.90 (d, 1H), 7.30 (s, 1H), 7.95 (s, 1 H), 11.9 (br s, 1 H); m/z 277 (M+H); HRMS (M+H) calculated for $C_{16}H_{13}N_4O$: 277.1089, found 277.1078.

EXAMPLE 94

[000182] This illustrates the production of 2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000183] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (248 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.75-2.90 (m, 4H), 6.73 (dd, 1 H), 6.88 (d, 1H), 7.92 (s, 1H), 7.95 (d, 1H); m/z 278 (M+H); HRMS (M+H) calculated for $C_{15}H_{12}N_5O$: 278.1042, found 278.1058.

EXAMPLE 95

[000184] This illustrates the production of 2-amino-4-(2-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate.

[000185] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (49.1 mg, 4% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.38-2.48 (m, 2H), 2.75-2.82 (m, 2H), 7.25-7.30 (m, 2H), 7.35-7.47 (m, 5H), 7.55-7.64 (m, 1H), 8.16-8.22 (m, 1H); m/z 316 (M+H);); HRMS (M+H) calculated for $C_{20}H_{15}FN_3$: 316.1250, found 316.1248.

EXAMPLE 96

[000186] This illustrates the production of 2-amino-3-cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid trifluoroacetate.

[000187] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (30.1 mg, 5% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.80-2.93 (m, 4H), 6.77 (dd, 1H), 6.98 (dd, 7.87 (dd, 1H), 7.92 (d, 1H), 7.95 (d, 1H), 7.99 (dd, 1H), 8.23 (d, 1H)); m/z 332 (M+H); HRMS (M+H) calculated for $C_{19}H_{14}N_3O_3$: 332.1035, found 332.1032.

EXAMPLE 97

[000188] This illustrates the production of 2-amino-3-cyano-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid bis(trifluoroacetate).

[000189] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (29.4 mg, 4% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.72-2.92 (m, 4H), 7.86 (s, 1H), 7.94 (d, 1H), 8.27 (d, 1H), 8.78 (br s, 1H); m/z 333 (M+H); HRMS (M+H) calculated for $C_{17}H_{13}N_6O_2$: 333.1100, found 333.1083.

EXAMPLE 98

[000190] This illustrates the production of 2-amino-4-(2-furyl)-5,6-dihydro-1,8-phenanthroline-3-carbonitrile bis(trifluoroacetate).

[000191] 2-amino-4-(2-furyl)-5,6-dihydro-1,8-phenanthroline-3-carbonitrile bis(trifluoroacetate) was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (205 mg, 12% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.85-2.98 (m, 4H), 6.79 (dd, 1H), 7.04 (dd, 1H), 8.02 (dd, 1H), 8.19 (1H), 8.76 (d, 1H), 8.77 (s, 1H); m/z 289 (M+H); HRMS (M+H) calculated for $C_{17}H_{13}N_4O$: 289.1089, found 289.1069.

EXAMPLE 99

[000192] This illustrates the production of 2-amino-4-(2-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000193] 2-amino-4-(2-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate) was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a yellow solid (173.7 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.50-2.60 (m, 2H), 2.72-2.78 (m, 2H), 7.36-7.48 (m, 3H), 7.55-7.63 (m, 1H), 7.97 (s, 1H); m/z 306 (M+H); HRMS (M+H) calculated for $C_{17}H_{13}FN_5$: 306.1150, found 306.1178.

EXAMPLE 100

[000194] This illustrates the production of 2-amino-4-phenyl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000195] This material was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a yellow solid (242 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.50-2.62 (m, 2H), 2.69-2.76 (m, 2H), 7.36-7.46 (m, 2H), 7.50-7.59 m, 3H), 7.96 (s, 1H); m/z 288 (M+H); HRMS (M+H) calculated for $C_{17}H_{14}N_5$: 288.1244, found 288.1253. TNFα release assay IC_{50} = 17.7 μM.

EXAMPLE 101

[000196] This illustrates the production of 2-amino-3-cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid trifluoroacetate.

[000197] Step- 1: (Preparation of 5-oxo-5,6,7,8-tetrahydronaphthalene-2-yl-trifluoromethanesulfonate) - A round bottomed flask was charged with 6-hydroxy-1-tetralone (7.87 g, 48.5 mmol), pyridine (97 mL) and a magnetic stirring bar. The flask was sealed under nitrogen, and triflic anhydride (8.24 mL, 49 mmol) was added dropwise over 30 minutes. The mixture was stirred at room temperature for 7 days, then the mixture was diluted with diethyl ether. The organic layer was washed with water (1X100 ml), 5% aqueous hydrogen chloride (2X100 mL), and brine (1X100 mL). The organic layer was then dried over magnesium sulfate and concentrated in vacuo. The product was purified via flash column chromatography (0-20% ethyl acetate/hexane) to give 11.72 g of product as a white solid (81% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.22 (quintet, 2H), 2.72 (t, 2H), 3.06 (t, 2H), 7.22 (s, 1H), 7.24 (d, 1H), 8.17 (d, 1H); HRMS (M+H) calculated for $C_{17}H_{10}F_3O_5S$: 295.0246, found 295.0285.

[000198] Step 2: (Preparation of methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate) - A three-necked round bottomed flask was charged with 5-oxo-5,6,7,8-tetrahydronaphthalene-2-yl-trifluoromethanesulfonate, prepared as described in Step 1, (9.98 g, 33.9 mmol), bis(diphenylphosphonyl)propane (0.42 4, 1 mmol), palladium acetate (0.23 g, 1 mmol), methanol (34 mL), dimethylformamide (68 mL), triethylamine (9.5 mL, 68.3 mmol) and a magnetic stirring bar. The flask was fitted with a condenser and septa, then carbon monoxide was bubbled

through the solution for 15 minutes. The flask was placed under a nitrogen atmosphere and heated to 70 degrees Celsius for 8 hours. The mixture was diluted with ethyl acetate (200 mL) and washed with water (1X100 mL), 5% aqueous hydrogen chloride (2X200 mL) and brine (1X100 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (0-30% ethyl acetate/hexane) to give 4.08 g of product as a yellow solid (59% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.21 (quintet, 2H), 2.74 (t, 2H), 3.06 (t, 2H), 3.98 (S, 3h), 7.30 (s, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.12 (d, 1H); m/z 205 (M+H); HRMS (M+H) calculated for $C_{12}H_{13}O_3$: 205.0859, found 205.0882.

[000199] Step 3: (Preparation of 2-amino-3-cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-8-carboxylic acid trifluoroacetate) - A glass vial was charged with methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate, as prepared in Step 2, above, (1.03 g, 5.06 mmol), malononitrile (0.363, 5.5 mmol), 2-furaldehyde (0.42 mL, 5.07 mmol), ammonium acetate (0.794 g, 10.3 mmol), toluene (10 mL) and a magnetic stirring bar. The vial was capped and heated to 80 degrees Celsius for 24 hours. The vial was cooled to room temperature, then the reaction mixture was diluted with a 1:1 mixture of dichloromethane/methanol (20 mL), and amberlyst resin (20 g) was added to the flask. The slurry was agitated for 72 hours at room temperature, then the resin was collected by vacuum filtration and washed with dichloromethane (3x30 mL). The resin was then combined with 2 M ammonia in methanol and agitated for 4 hours at room temperature. The resin was filtered and washed with a 1:1 mixture of dichloromethane/2M ammonia in methanol (6X30 mL). The combined filtrates were concentrated in vacuo. The residue was treated with ethanol (6 mL) and 2 M aqueous lithium hydroxide (6 mL), at 50 degrees Celsius for 1 hour. The mixture was concentrated in vacuo, and the residue purified by preparative RP-HPLC giving 0.3 g of product as a white solid (18% yield). ^{1}H NMR (300 MHz, DMSO) δ 2.80-2.96 (m, 4H), 6.79 (m, 1H), 7.00 (d, 1H), 7.89 (s, 1H), 7.95 (d, 1H), 8.01 (s, 1H), 8.26 (s, 1H); m/z

332 (M+H); HRMS (M+H) calculated for $C_{19}H_{14}N_3O_3$: 332.1030, found 332.1039.

EXAMPLE 102

[000200] This illustrates the preparation of 2-amino-4-(2,3-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000201] 2-amino-4-(2,3-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate) was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 106. The product was isolated as a yellow solid (205.7 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.55-2.60 (m, 2H), 2.72-2.80 (m, 2H), 6.81 (br s, 1H), 7.25-7.32 (m, 1H), 7.38-7.46 (m, 1H), 7.58-7.68 (m, 1H), 7.97 (s, 1H); m/z 324 (M+H); HRMS (M+H) calculated for $C_{17}H_{12}F_2N_5$: 324.1055, found 324.1030. TNFα release assay IC_{50} = 4.0 μM; Rat LPS Assay 83% inhibition at 20 mpk (IG).

EXAMPLE 103

[000202] This illustrates the preparation of 2-amino-4-(2,4-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000203] 2-amino-4-(2,4-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate) was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a yellow solid (149.1 mg, 13% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.55-2.60 (m, 2H), 2.72-2.80 (m, 2H), 6.78 (br s, 1H), 7.31 (td, 1H), 7.47-7.58 (m, 2H), 7.96 (s, 1H); m/z 324 (M+H); HRMS (M+H) calculated for $C_{17}H_{12}F_2N_5$: 324.1055, found 324.1074.

EXAMPLE 104

[000204] This illustrates the preparation of 2-amino-4-(2,6-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate).

[000205] 2-amino-4-(2,6-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate) was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a white solid (137.7 mg, 12% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.55-2.60 (m, 2H), 2.72-2.80 (m, 2H), 6.85 (br s, 1H), 7.33-7.40 (m, 2H), 7.62-7.73 (m, 1H), 7.98 (s, 1H); m/z 324 (M+H); HRMS (M+H) calculated for $C_{17}H_{12}F_2N_5$: 324.1055, found 324.1098.

EXAMPLE 105

[000206] This illustrates the preparation of 8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile.

[000207] 8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a yellow solid (51 mg, 8% yield). ^{1}H NMR (400 MHz, DMSO) δ 2.67 (t, 2H), 2.83 (t, 2H), 6.76 (dd, 1H), 6.93 (d, 1H), 7.57 (s, 1H), 7.98 (d, 1H); m/z 278 (M+H); HRMS (M+H) calculated for $C_{157}H_{12}N_5O$: 278.101036, found 278.1051. TNFα release assay IC_{50} = 0.9 μM.

EXAMPLE 106

[000208] This illustrates the preparation of 2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile trifluoroacetate.

[000209] 2-amino-4-(2-furyl)-6-(1H-pyrazol-3-yl)nicotinonitrile trifluoroacetate was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a brown solid (110 mg, 6% yield). ^{1}H NMR (300 MHz, DMSO) δ 6.76 (dd,

1H), 6.84 (br s, 1H), 6.95 (s, 1H), 7.46 (d, 1H), 7.64 (s, 1H), 7.86 (s, 1H), 8.03 (s, 1H); m/z 253 (M+H); HRMS (M+H) calculated for $C_{13}H_{10}N_5O$: 252.0880, found 252.0855. TNFα release assay IC_{50} = 4.0 μM.

EXAMPLE 107

[000210] This illustrates the preparation of 8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile trifluoroacetate.

[000211] 8-amino-6-(2-furyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-7-carbonitrile trifluoroacetate was prepared in a manner similar to that used to produce 2-amino-4-(2-furyl)-8-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate, as described in Example 92. The product was isolated as a tan solid (379 mg, 38% yield). ^{1}H NMR (300 MHz, DMSO) δ 2.69 (t, 2H), 2.84 (t, 2H), 6.76 (dd, 1H), 6.94 dd, 1H), 7.58 (s, 1H), 7.99 (dd, 1H); m/z 278 (M+H); HRMS (M+H) calculated for $C_{15}H_{12}N_5O$: 278.1036, found 278.1054.

EXAMPLES 108 - 174

[000212] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000213] The compounds listed in the table below were prepared by the methods described in Kambe, S. *et al.*, "A simple method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis 5*:366 - 368 (1980). NMR analysis was carried out for each compound and selected data is presented for each compound as shown in the table.

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
108	2-amino-4-(3-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	306	306.115	306.1168	$C_{17}H_{13}FN_5$
109	*N*-{4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]phenyl}methanesulfonamide trifluoroacetate	355	355.0859	355.0853	$C_{17}H_{15}N_4O_3S$
110	2-amino-4-(2-furyl)-6,7-dihydro-5H-pyrrolo[2,3-h]quinoline-3-carbonitrile trifluoroacetate	377	277.1089	277.1063	$C_{16}H_{13}N_4O$
111	2-amino-4-(4-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	318	318.1349	318.1349	$C_{18}H_{16}N_5O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
112	2-amino-4-(2,5-difluorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	324	324.1055	324.1098	$C_{17}H_{12}F_2N_5$
113	2-amino-4-(4-fluorophenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	306	306.115	306.1155	$C_{17}H_{13}FN_5$
114	2-amino-4-(4H-1,2,4-triazol-3-yl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile bis(trifluoroacetate)	289	289.1202	289.1173	$C_{16}H_{13}N_6$
115	2-amino-6-(4-methoxyphenyl)-4-(4H-1,2,4-triazol-3-yl)nicotinonitrile bis(trifluoroacetate)	293	293.1151	293.1137	$C_{15}H_{13}N_6O$
116	2-amino-4-(2-fluorophenyl)-6-(3-furyl)nicotinonitrile trifluoroacetate	280	280.0881	280.0916	$C_{16}H_{11}FN_3O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
117	8-amino-6-(2-furyl)-4,5-dihydro-2H-pyrazolo[4,3-h]quinoline-7-carbonitrile	278	278.1036	278.1018	$C_{15}H_{12}N_5O$
118	2-amino-4-(3-methoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	318	318.1349	318.1361	$C_{18}H_{16}N_5O$
119	2-amino-4-(2-furyl)-7-methyl-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	292	292.1198	292.1201	$C_{16}H_{14}N_5O$
120	*N*-[4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenyl]acetamide bis(trifluoroacetate)	303	303.1353	303.1399	$C_{19}H_{17}N_6O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
121	6-amino-4-[(4-methoxyphenyl)amino]-2-(trifluoromethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	351	351.1063	351.1078	$C_{16}H_{14}F_3N_4O_2$
122	4,6-diamino-2-ethyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	205	205.1089	205.1056	$C_{10}H_{13}N_4O$
123	3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	332	332.1142	332.1148	$C_{18}H_{14}N_5O_2$
124	2-amino-4-(1,3-benzodioxol-4-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	332	332.1142	332.1124	$C_{18}H_{14}N_5O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
125	4,6-diamino-2-methyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	191	191.0933	191.0896	$C_9H_{11}N_4O$
126	2,8-diamino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	303	303.1246	303.1237	$C_{18}H_{15}N_4O$
127	4,6-diamino-2-butyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	233	233.1402	233.1378	$C_{12}H_{17}N_4O$
128	2-amino-4-(4-cyanophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	313	313.1196	313.1244	$C_{18}H_{13}N_6$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
129	2-amino-4-(2-chlorophenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	322	322.0854	322.089	$C_{17}H_{13}ClN_5$
130	2-amino-4-pyridin-3-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile tris(trifluoroacetate)	289	289.1196	289.1209	$C_{16}H_{13}N_6$
131	2-amino-4-(2-furyl)-7-hydroxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	304	304.1086	304.1076	$C_{18}H_{14}N_3O_2$
132	2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile trifluoroacetate	301	301.1084	301.1078	$C_{18}H_{13}N_4O$
133	2-amino-4-pyridin-4-yl-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile tris(trifluoroacetate)	289	289.1196	289.1218	$C_{16}H_{13}N_6$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
134	2-amino-4-[2-(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	354	354.1161	354.1162	$C_{18}H_{14}F_2N_5O$
135	4,6-diamino-2-[(prop-2-ynyloxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	245	245.1039	245.1019	$C_{12}H_{13}N_4O_2$
136	2-[(allyloxy)methyl]-4,6-diamino-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	247	247.1195	247.1179	$C_{12}H_{15}N_4O_2$
137	4,6-diamino-2-(methoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	221	221.1039	221.1015	$C_{10}H_{13}N_4O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
138	2-amino-4-(2-furyl)-6-methyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	302	302.1293	302.1269	$C_{19}H_{16}N_3O$
139	4,6-diamino-2-(isopropoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	249	249.1352	249.1336	$C_{12}H_{17}N_4O_2$
140	4,6-diamino-2-(ethoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	235	235.1195	235.118	$C_{11}H_{15}N_4O_2$
141	4,6-diamino-2-[(1,1,2,2-tetrafluoroethoxy)methyl]-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	307	307.0813	307.0819	$C_{11}H_{11}F_4N_4O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
142	2-amino-4-(2-methoxyphenyl)-6,8-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	318	318.1349	318.1357	$C_{18}H_{16}N_5O$
143	4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	332	332.1142	332.1153	$C_{18}H_{14}N_5O_2$
144	4,6-diamino-2-(tert-butoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	263	263.1503	263.1506	$C_{13}H_{19}N_4O_2$
145	methyl 3-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	346	346.1299	346.1318	$C_{19}H_{16}N_5O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
146	4,6-diamino-3-phenyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	253	253.1038	253.1082	$C_{14}H_{13}N_4O$
147	4,6-diamino-3-vinyl-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	203	203.0933	203.0904	$C_{10}H_{11}N_4O$
148	4,6-diamino-2-(phenoxymethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile trifluoroacetate	283	283.1167	283.1195	$C_{15}H_{15}N_4O_2$
149	2-amino-4-(2-furyl)-7,9-dimethyl-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	316	316.145	316.1441	$C_{20}H_{18}N_3O$
150	2-amino-4-(2-furyl)-7-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	318	318.1243	318.124	$C_{19}H_{16}N_3O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
151	2-amino-4-(2-furyl)-8,9-dimethoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	348	348.1348	348.1351	$C_{20}H_{18}N_3O_3$
152	2-amino-4-(2-furyl)-8-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	318	318.1243	318.1232	$C_{19}H_{16}N_3O_2$
153	2-amino-4-(2-furyl)-9-methoxy-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	318	318.1243	318.1243	$C_{19}H_{16}N_3O_2$
154	2-amino-4-(2-furyl)-5H-indeno[1,2-b]pyridine-3-carbonitrile trifluoroacetate	274	274.098	274.1051	$C_{17}H_{12}N_3O$
155	2-amino-4-(2-furyl)-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile trifluoroacetate	302	302.1293	302.1285	$C_{19}H_{16}N_3O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
156	2-amino-4-(3-fluorophenyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	316	316.125	316.149	$C_{20}H_{15}FN_3$
157	2-amino-4-(2-ethoxyphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	332	332.1506	332.1507	$C_{19}H_{18}N_5O$
158	methyl [2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetate bis(trifluoroacetate)	376	376.1404	376.1403	$C_{20}H_{18}N_5O_3$
159	4-[2-(allyloxy)phenyl]-2-amino-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	344	344.1506	344.1507	$C_{20}H_{18}N_5O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
160	2-amino-4-[2-(beta-D-glucopyranosyloxy) phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	466	466.1721	466.1742	$C_{23}H_{24}N_5O_6$
161	2-amino-4-[2-(hexyloxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	388	388.2132	388.2136	$C_{23}H_{26}N_5O$
162	methyl 2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	346	346.1299	346.1345	$C_{19}H_{16}N_5O_2$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
163	2-amino-4-(1H-indol-7-yl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	327	327.1353	327.164	$C_{19}H_{15}N_6$
164	methyl 4-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoate bis(trifluoroacetate)	346	346.1299	346.1329	$C_{19}H_{16}N_5O_2$
165	2-amino-4-[4-(dimethylamino)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	331	331.1666	331.1684	$C_{19}H_{19}N_6$
166	2-amino-4-(2-methylphenyl)-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	302	302.14	302.1408	$C_{18}H_{16}N_5$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
167	2-amino-4-[2-(2-hydroxyethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	348	348.1455	348.149	$C_{19}H_{18}N_5O_2$
168	2-amino-4-{4-[(2-cyanoethyl)(methyl)amino]phenyl}-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	370	370.1775	370.1754	$C_{21}H_{20}N_7$
169	2-amino-4-(2-furyl)-5H-thiochromeno[4,3-b]pyridine-3-carbonitrile trifluoroacetate	306	306.0696	306.07	$C_{17}H_{12}N_3OS$
170	2-amino-4-[2-(trifluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile bis(trifluoroacetate)	372	372.1067	372.1095	$C_{18}H_{13}F_3N_5O$

Ex. No.	Compound Name	m/z (M+H)	HRMS Theor.	HRMS Found	Calculated Formula
171	[2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)phenoxy]acetic acid bis(trifluoroacetate)	362	362.1248	362.1233	$C_{19}H_{16}N_5O_3$
172	2-(2-amino-3-cyano-6,7-dihydro-5H-pyrazolo[3,4-h]quinolin-4-yl)benzoic acid bis(trifluoroacetate)	332	332.1142	332.1131	$C_{18}H_{14}N_5O_2$
173	2-amino-4-[2-(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrazolo[3,4-h]quinoline-3-carbonitrile	354	354.1161	354.1163	$C_{18}H_{14}F_2N_5O$
174	4,6-diamino-2-(morpholin-4-ylmethyl)-2,3-dihydrofuro[2,3-b]pyridine-5-carbonitrile	276	276.1455	276.1455	$C_{13}H_{18}N_5O_2$

EXAMPLE 175

[000214] This illustrates the preparation of 4-[6-amino-5-cyano-4-(2-furyl)pyridin-2-yl]benzoic acid trifluoroacetate.

[000215] A glass vial was charged with 4-acetylbenzoic acid (0.33 g, 2 mmol), malononitrile, (0.12 g, 3 mmol), ammonium acetate (0.23 g, 6 mmol), furaldehyde (0.19 g, 3 mmol) and a magnetic stirring bar. Toluene (3 mL) was added to the vial, which was capped and heated to 80 degrees Celsius for 18 hours. The vial was then cooled to room temperature, and a 1:2 mixture of methanol and dichloromethane (15 mL) was added followed by 8 g of Amberlyst resin. The mixture was agitated for 24 h, then the resin was filtered and washed with dichloromethane (3X15 mL). A 2 M solution of ammonia in methanol (15 mL) was added to the resin, and the mixture was agitated overnight at room temperature. The resin was filtered and the filtrate collected in a tared flask. The resin was washed sequentially with a 1:1 mixture of methanol and dichloromethane (2X15 mL), 2 M ammonia in methanol (2X15 mL), and a 1:1 mixture of methanol and dichloromethane (2X15 mL). The combined filtrates were concentrated in vacuo, and the residue was purified by reverse phase chromatography. The product was isolated as a tan solid (9.1 mg, 1% yield). ^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD) δ 6.60 (dd, 1H), 7.49 (d, 1H), 7.54 (s, 1H), 7.663 (d, 1H), 8.02 (d, 2H), 8.12 (d, 2H); m/z 306 (M+H); HRMS (M+H) calculated for $C_{17}H_{13}N_3O_3$: 306.0879, found 306.0874.

EXAMPLES 176 - 213

[000216] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000217] The compounds listed in the table below were prepared by the methods described in Kambe, S. *et al.,* "A simple method for the preparation of 2-amino-4-aryl-3-cyanopyridines by the condensation of malononitrile with aromatic aldehydes and alkyl ketones in the presence of ammonium acetate", *Synthesis 5*:366 - 368 (1980). NMR analysis was carried out for each compound and selected data is presented for each compound as shown in the table.

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
176	2-amino-4-(2-furyl)-6-propyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile bis(trifluoroacetate)	283	283.1559	283.1577	$C_{16}H_{19}N_4O$
177	2-amino-4-(2-furyl)-6-[4-(trifluoromethoxy)phenyl]nicotinonitrile trifluoroacetate	346	346.0803	346.0831	$C_{17}H_{11}F_3N_3O_2$
178	2-amino-4-(2-furyl)-6-methyl-5-phenylnicotinonitrile trifluoroacetate	276	276.1137	276.116	$C_{17}H_{14}N_3O$
179	2-amino-6-benzyl-4-(2-furyl)nicotinonitrile trifluoroacetate	276	276.1137	276.117	$C_{17}H_{14}N_3O$
180	2-amino-4-(2-furyl)-6-isobutyl-nicotinonitrile	242	242.1293	242.1319	$C_{14}H_{16}N_3O$
181	2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-quinoline-3-carbonitrile	240	240.1137	240.1154	$C_{14}H_{14}N_3O$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
182	2-amino-5-(4-fluorophenyl)-4-(2-furyl)-6-methylnicotinonitrile trifluoroacetate	294	294.1043	294.1053	$C_{17}H_{13}FN_3O$
183	2-amino-6-(4-fluorobenzyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	294	294.1043	294.1063	$C_{17}H_{13}FN_3O$
184	2-amino-6-(4-fluorophenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	280	280.0886	280.0904	$C_{16}H_{11}FN_3O$
185	2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-3-carbonitrile trifluoroacetate	252	252.1137	252.1136	$C_{15}H_{14}N_3O$
186	2-amino-6-(3,4-dimethylphenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	290	290.1293	290.1292	$C_{18}H_{16}N_3O$
187	2-amino-4-(2-furyl)-5,6-dihydrobenzo[h]quinoline-3-carbonitrile trifluoroacetate	288	288.1137	288.1139	$C_{18}H_{14}N_3O$

Ex. No.	Compound name	m/z (M+H)	HRMS Th or.	HRMS Found	Formula Calcd for
188	2-amino-4-(2-furyl)-5-methyl-6-phenylnicotinonitrile trifluoroacetate	276	276.1137	276.1143	$C_{17}H_{14}N_3O$
189	2-amino-4-(2-furyl)-5,6-diphenylnicotinonitrile trifluoroacetate	338	338.1293	338.1294	$C_{22}H_{16}N_3O$
190	2-amino-6-(4-fluorophenyl)-4-(2-furyl)-5-methylnicotinonitrile trifluoroacetate	294	294.1043	294.1044	$C_{17}H_{13}FN_3O$
191	2-amino-4-(2-furyl)-6-(4-methoxyphenyl)-5-methylnicotinonitrile trifluoroacetate	306	306.1243	306.1235	$C_{18}H_{16}N_3O_2$
192	2-amino-4-(2-furyl)-6-(3-hydroxyphenyl)nicotinonitrile trifluoroacetate	278	278.093	278.093	$C_{16}H_{12}N_3O_2$
193	2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)-5-methylnicotinonitrile trifluoroacetate	292	292.1086	292.1086	$C_{17}H_{14}N_3O_2$

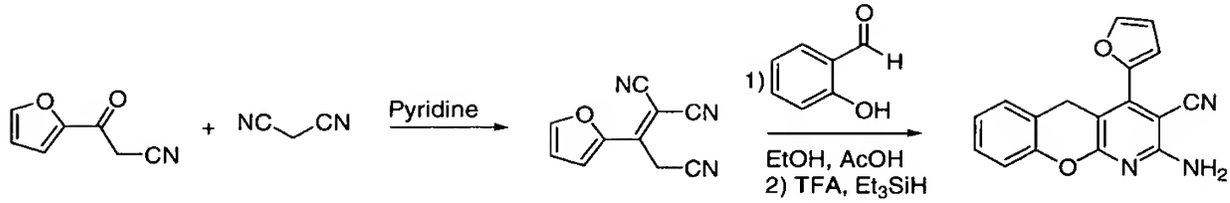
Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
194	2-amino-4-(2-furyl)-6-(4-hydroxyphenyl)nicotinonitrile trifluoroacetate	278	278.093	278.0934	$C_{16}H_{12}N_3O_2$
195	2-amino-4-(2-furyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile bis(trifluoroacetate)	241	241.1089	241.1076	$C_{13}H_{13}N_4O_2$
196	2-amino-4-(2-furyl)-6-(8-hydroxy-1-naphthyl)nicotinonitrile trifluoroacetate	328	328.1086	328.1095	$C_{20}H_{14}N_3O_2$
197	ethyl 2-amino-3-cyano-4-(2-furyl)-5,6,7,8-tetrahydroquinoline-6-carboxylate trifluoroacetate	312	312.1348	312.1342	$C_{17}H_{18}N_3O_2$
198	2-amino-6-(4-cyanophenyl)-4-(2-furyl)nicotinonitrile trifluoroacetate	287	287.0933	287.0941	$C_{17}H_{11}N_4O$
199	2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-2-yl)nicotinonitrile	265	265.1089	265.1123	$C_{15}H_{13}N_4O$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
200	2-amino-4,6-di(2-furyl)nicotinonitrile	252	252.0773	252.0751	$C_{14}H_{10}N_3O_3$
201	2-amino-4-(2-furyl)-6-(1H-pyrrol-2-yl)nicotinonitrile	251	251.0933	251.0928	$C_{14}H_{11}N_4O$
202	2-amino-4-(2-furyl)-6-[4-(1H-imidazol-1-yl)phenyl]nicotinonitrile	328	328.1198	328.1194	$C_{19}H_{14}N_5O$
203	2-amino-4-(2-furyl)-6-(1,3-thiazol-2-yl)nicotinonitrile bis(trifluoroacetate)	269	269.0497	269.0479	$C_{13}H_9N_4O$
204	2-amino-4-(2-furyl)-6-thien-3-ylnicotinonitrile	268	268.0545	268.0545	$C_{14}H_{10}N_3O$
205	2-amino-6-(1,3-benzodioxol-5-yl)-4-(2-furyl)nicotinonitrile	306	306.0879	306.0888	$C_{17}H_{12}N_3O_3$
206	6-amino-4-(2-furyl)-2,2'-bipyridine-5-carbonitrile bis(trifluoroacetate)	326	263.0933	263.0945	$C_{15}H_{11}N_4O$
207	6-amino-4-(2-furyl)-2,3'-bipyridine-5-carbonitrile	263	263.0933	263.0935	$C_{15}H_{11}N_4O$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
208	6-amino-4-(2-furyl)-2,4'-bipyridine-5-carbonitrile bis(trifluoroacetate)	263	263.0933	263.0928	$C_{15}H_{11}N_4O$
209	2-amino-4-(2-furyl)-6-phenylnicotinonitrile	262	262.098	262.0971	$C_{16}H_{12}N_3O$
210	2-amino-4-(2-furyl)-6-(4-methylphenyl)nicotinonitrile	276	276.1137	276.1121	$C_{17}H_{14}N_3O$
211	2-amino-4-(2-furyl)-6-(1-methyl-1H-pyrrol-3-yl)nicotinonitrile	265	265.1089	265.1088	$C_{15}H_{13}N_4O$
212	2-amino-4-(2-furyl)-6-(1H-indol-3-yl)nicotinonitrile	301	301.1089	301.1107	$C_{18}H_{13}N_4O$
213	2-amino-4-(2-furyl)benzo[h]quinoline-3-carbonitrile trifluoroacetate	286	----	----	$C_{18}H_{12}N_3O$

EXAMPLE 214

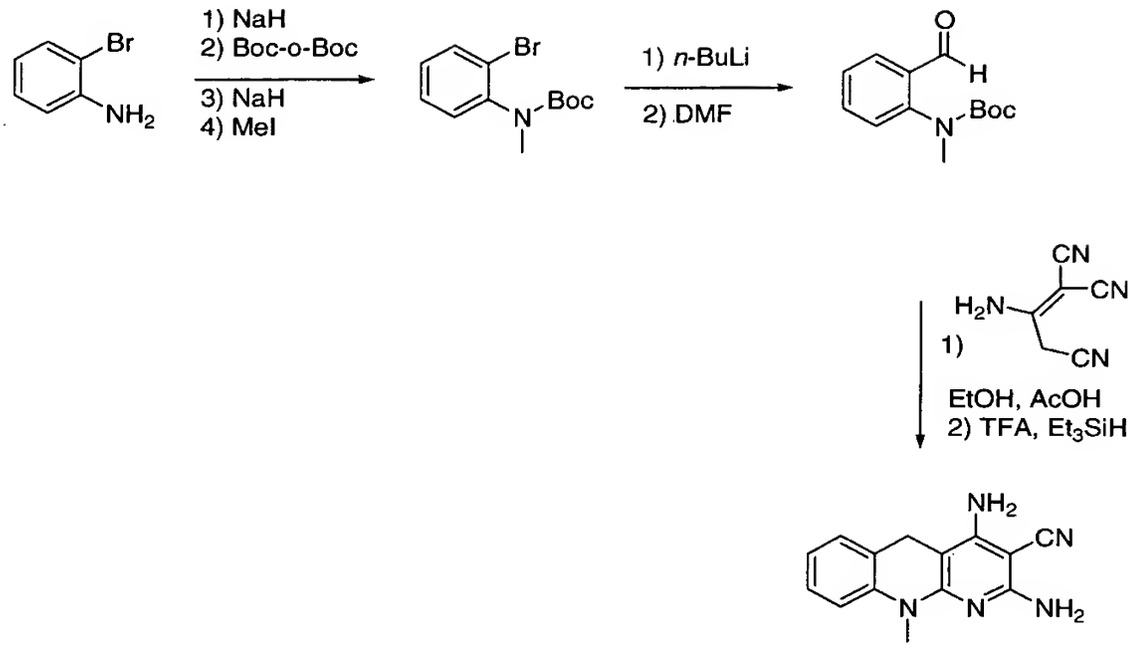
[000218] This illustrates the production of 2-amino-4-(2-furyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



[000219] 3-(2-furyl)-3-oxopropanenitrile (10 mmol, 1.0 equiv., 1.35g) and malononitrile (10 mmol, 1.0 equiv., 600μL) were combined in pridine (10mL). The mixture was heated to 100 °C for 1 hour. The reaction mixture was diluted with 150 mL dichloromethane and washed with 1 M HCl (3 x 50 mL). The organic layer was dried and evaporated to give a dark oil (GDS-13695-130). The oil was dissolved in EtOH (30 mL) and treated with salicaldehyde (10 mmol, 1.0 equiv., 1.0 mL) and acetic acid (AcOH) (10 mL). The resulting mixture was heated to reflux for 2 hours. The solvents were evaporated and the *in vacuo* and the residue was dissolved in trifluoroacetic acid (15mL). Triethylsilane (10 mL) was added and the solution was stirred overnight. The solvents were evaporated and the residue purified by reverse phase chromatography. The product was isolated as a solid (370mg, 13%). ^{1}H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.24-7.20 (m, 2H), 7.08-7.04 (m, 3H), 6.94 (bs, 2H), 6.76 (s, 1H), 3.96 (s, 2H): m/z 290 (M+H).

EXAMPLE 215

[000220] This illustrates the production of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate.



[000221] Step 1: (synthesis of *t*-Butyl 2-bromophenyl(methyl)carbamate)

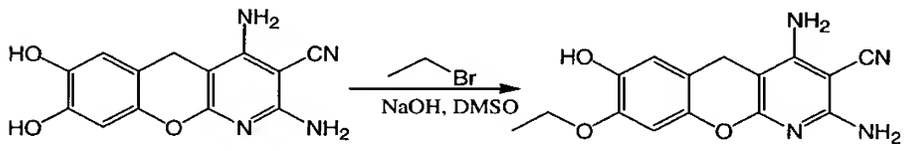
[000222] 2-bromoaniline (25 mmol, 1.0 equiv. 4.3g) was dissolved in THF (150 mL). Sodium hydride (60% in mineral oil, 1.1g) was added and the mixture heated to reflux for 1 hour. After cooling to room temperature, a solution of di-*t*-butyl-dicarbonate in THF (1.0M, 30 mmol, 1.2 equiv., 30 mL) was added followed by sodium hydride (1.1g). The resulting mixture was heated to reflux for 14 hours. After cooling to room temperature, Iodomethane (28 mmol, 1.12 equiv., 1.75 mL) was added and the mixture heated to reflux for 3 hours. After cooling to room temperature, the reaction was quenched with water and diluted with ether. The organic layer was washed with saturated aqueous ammonium chloride (NH_4Cl), saturated aqueous sodium bicarbonate ($NaHCO_3$), and saturated aqueous sodium chloride (NaCl). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. Purification by silica gel chromatography gave the product as a yellow oil (5.9g, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H), 7.29 (t, 1H), 7.21 (d, 1H), 7.12 (t, 1H), 3.13 (s, 3H), 1.33 (s, 9H): m/z 271 (M+H).

[000223] Step 2: (synthesis of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate)

[000224] *t*-Butyl 2-bromophenyl(methyl)carbamate (2.65 mmol, 1.0 equiv., 759 mg) was dissolved in THF (20 mL). The solution was cooled in a dry ice acetone bath and a solution of *n*-BuLi in hexane (1.6M, 1.1 equiv. 1.8 mL) was added dropwise. After 15 minutes, dimethylformamide (DMF) (1 mL) was added and the reaction allowed to warm to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl, and partitioned between ether and water. The organic layer was washed with water and dried over $MgSO_4$, filtered and evaporated to get 820 mg of a yellow oil. This oil was carried on immediately without purification or characterization. The resulting oil was treated with 2-amino-1-propene-1,1,3-tricarbonitrile (2 mmol, 265mg), acetic acid (2.0mL), and ethanol (10mL) and the resulting solution was heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (7mL) at 0°C. Triethylsilane (5.0mL) was added via syringe. The reaction stirred for 2 hours before evaporating solvents to get a brown solid. The solid was washed with dichloromethane and dried to give the product as a light brown solid. (90mg, 9%). ^{1}H NMR (400 MHz, DMSO) δ 7.16 (t, 1H), 7.03 (d, 1H), 6.97-6.91 (m, 2H), 3.70 (s, 2H), 3.34 (s, 3H): m/z 252 (M+H).

EXAMPLE 216

[000225] This illustrates the production of 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



[000226] 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (400 mg, 1.0 mmol) and NaOH (166 mg, 4.2 mmol) were suspended in dimethylsulfoxide (DMSO) (5 mL) and warmed until dissolved. Ethyl bromide was added to the reaction mixture, which was heated to 85°C until disappearance of starting material (HPCL monitoring). After neutralizing with NH_4Cl, the crude reaction mixture was purified by

reverse phase column chromatography. Evaporation of the solvent on a lyophilizer gave an orange solid as a TFA salt 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, which was confirmed by 2D NMR analysis. ^{1}H-NMR (300 MHz, CD3OD): δ 1.47 (t, 3H), 3.63 (s, 2H), 4.12 (quartet, 2H), 6.59-6.81 (m, 2H). HRMS calcd for C15H14N4O3 (M+H): 299.11. Found: 299.1132.

EXAMPLE 217

[000227] This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000228] 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same method as described above in Example 216, using 2-bromoethyl-ethylether in lieu of 2-bromoethyl-ethylether. ^{1}H-NMR (300 MHz, CD3OD): δ 1.28 (t, 3H), 3.60 (s, 2H), 3.67 (quartet, 2H), 3.86 (s, 2H), 4.19 (s, 2H), 6.58-6.82 (m, 2H). HRMS calcd for C17H18N4O4 (M+H): 343.13. Found: 343.1418.

EXAMPLES 218 - 219

[000229] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000230] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 216. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	HRMS calcd	HRMS found
218	tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	499.21	499.2204
219	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351.14	351.1445

EXAMPLE 220

[000231] This illustrates the production of 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000232] To a cooled (0 °C) solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34mmol, 400mg) and dichloromethane (4.0mL) was slowly added boron tribromide (1M, dichloromethane, 8.04mmol, 8.04mL). The suspension was stirred at 0 °C for 15 minutes, then the ice bath was removed and the reaction warmed to 23 °C overnight. After 16h at 23 °C the reaction was cooled to 0°C and carefully neutralized with 2.5N sodium hydroxide to pH = 7. The product was collected by filtration, dissolved in dimethyl sulfoxide (1.0 mL) and purified by reverse phase chromatography. The product was isolated as a pale orange solid (62mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.071(s, 1H), 8.795 (s, 1H), 6.520 (s, 1H), 6.410 (bs, 2H), 6.405(s, 1H), 6.244 (bs, 2H), 3.48 (s, 2H): m/z 271 (M+); HRMS (M+H) calculated for $C_{13}H_{11}N_4O_3$ 271.0753, found 271.0721.

EXAMPLE 221

[000233] This illustrates the production of 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000234] 2,4-Dihydroxy-benzaldehyde (43.4mmol, 6.0g), 2-amino-1-propene-1,1,3-tricarbonitrile (43.4mmol, 5.74g), acetic acid (13.0mL), and ethanol (125.0mL) were combined and heated to reflux for 2 hours. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (160.0mL) at 0°C. Triethylsilane (0.28mol, 32.76g, 45.0mL) was added via syringe. The reaction was stirred for 1 hour at 0°C. 300mL of dichloromethane was added to the reaction and the solid was collected via filtration and washed (2x75mL) with dichloromethane and ether. The product was isolated as a pale orange solid (13.10g, 63% yield). ^{1}H NMR (400 MHz, DMSO) δ 6.958(d, 1H), 6.537 (dd, 1H), 6.390 (d, 1H), 3.510(s, 2H): m/z 255 (M+); HRMS (M+H) calculated for $C_{13}H_{11}N_4O_2$ 255.0804, found 255.0894.

EXAMPLE 222

[000235] This illustrates the production of 8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile.

[000236] 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.56mmol, 150mg) was dissolved in DMSO (3.0mL) and sodium hydroxide (2.24mmol, 90mg) was added followed by dibromoethane (0.56mmol, 105.20mg, 48.26μL). The dark homogeneous solution was heated to 70°C for 16 hours. The crude reaction mixture was cooled to 23°C, neutralized with trifluoroacetic acid and directly purified via reverse phase chromatography. The product was isolated as a pale orange solid (30mg, 18% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 6.715(s, 1H), 6.553 (s, 1H), 4.215 (bs, 4H), 3.575(s, 2H): m/z 298 (M+H).

EXAMPLE 223

[000237] This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000238] 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.62mmol, 300mg) was dissolved in DMSO (4.0mL) and solid sodium hydroxide (2.79mmol, 111.6mg) was added followed by 2-bromoethyl-ethylether (0.62mmol, 69.9μL). The reaction was heated to

80°C with stirring for 9 hours. The crude reaction was filtered and diluted with DMSO (4.0mL) and purified via reverse phase chromatography. The product was isolated as a tan solid (80mg, 40% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.180(d, 1H), 6.795 (d, 1H), 6.46 (d, 1H), 4.090 (t, 2H), 3.766(t, 2H), 3.607 (s, 2H), 3.572 (t, 2H), 1.200 (t, 2H); m/z 327 (M+H).

EXAMPLE 224

[000239] This illustrates the production of 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile .

[000240] 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrilein the same manner as described in Example 223, using 1-(2-chloroethyl)pyridine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (100mg, 46% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.199 (d, 1H), 6.680 (d, 1H), 6.668 (d, 1H), 4.290 (t, 2H), 3.618 (s, 2H), 3.562 (t, 2H), 3.375 (bs, 4H), 2.077(bs, 4H); m/z 352 (M+H). TNFα release assay IC_{50}: 2.9μM; Rat LPS Assay 60% inhibition at 20 mpk (IP).

EXAMPLE 225

[000241] This illustrates the production of 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000242] 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 223 using 2-bromoethylamine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (167mg, 51% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.180 (bs, 2H), 7.100 (d, 1H), 6.762 (d, 1H), 6.646 (bs, 1H), 4.154 (t, 2H), 3.573 (s, 2H), 3.155 (t, 2H); m/z 398 (M+H). TNFα release assay IC_{50}: 6.9μM; Rat LPS Assay 88% inhibition at 20 mpk (IP).

EXAMPLE 226

[000243] This illustrates the production of [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid.

[000244] [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 223 using bromoacetic acid in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (110.6mg, 31% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.030 (d, 1H), 6.640 (d, 1H), 6.516 (d, 1H), 6.474 (bs, 2H), 6.278 (bs, 2H), 4.633 (s, 2H), 3.543 (s, 2H); m/z 427 (M+H).

EXAMPLE 227

[000245] This illustrates the production of 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000246] 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 223 using 2-bromoethanol in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (120mg, 35% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.025 (d, 1H), 6.670 (d, 1H), 6.550 (d, 1H), 3.931 (t, 2H), 3.662 (t, 2H), 3.546 (s, 2H); m/z 413 (M+H).

EXAMPLE 228

[000247] This illustrates the production of 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000248] 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 223 using 1-(2-chloroethyl)morpholine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (80mg, 17% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.071 (d, 1H), 6.714 (d, 1H), 6.654 (d, 1H), 6.527 (bs, 2H), 6.323 (bs, 2H), 4.311 (t, 2H), 3.938 (m, 2H), 3.664 (t, 2H), 3.558 (s, 2H), 3.534 (m, 2H), 3.451 (m, 2H), 3.158 (m, 2H); m/z 482 (M+H).

EXAMPLES 229 - 235

[000249] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000250] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 223. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	m/z (M+H)
229	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
230	7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	283
231	8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	295
232	2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	311
233	8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	339
234	2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	399
235	2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326

EXAMPLE 236

[000251] This illustrates the production of 2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate).

[000252] 3-Methoxysalicyaldehyde (10 mmol, 1.52 g), 2-amino-1-propene-1,1,3-tricarbonitrile (10 mmol, 1.32 g) acetic acid (2.5 mL), and ethanol (40 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (15 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL) was added via syringe. The reaction stirred for one hour at room temperature. Dichloromethane (100 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a white solid (2.5 g,

50% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.08 (t, J = 8Hz,1H), 7.00-6.80 (m, 2H), 6.73 (d, J = 7.4 Hz, 2H), 3.83(s, 3H), 3.68 (s, 2H); m/z 269 (M+H); Anal. calculated for $C_{14}H_{12}N_4O_2$-2CF_3CO_2H: C, 43.56; H, 2.84; N, 11.29, found: C, 43.40; H, 2.98; N, 11.32.

EXAMPLE 237

[000253] This illustrates the production of 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000254] 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 236, except that 5-hydroxysalicyaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a pink solid (951 mg, 30% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88 (d, J = 8.8 Hz, 1H), 6.63 (d, J=8.7 Hz, 1H), 6.55(s, 1H), 3.6 (s, 2H): m/z 255 (M+H); Anal. calculated for $C_{13}H_{10}N_4O_2$-1.5CF_3CO_2H -0.5H_2O: C, 44.25; H, 2.90; N, 12.90, found: C, 44.04; H, 3.05; N, 12.84.

EXAMPLE 238

[000255] This illustrates the production of 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

[000256] 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 236 except that salicyaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a light tan solid (1.26 g, 33% yield). ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.30-6.90 (m, 6H), 3.7 (s, 2H); m/z 239 (M+H); Anal. Calcd for $C_{13}H_{10}N_4O$-2CF_3CO_2H -0.25H_2O: C, 43.37; H, 2.68; N, 11.90, found: C, 43.07; H, 2.81; N, 11.79.

EXAMPLE 239

[000257] This illustrates the production of 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000258] 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 236, except that 2,3,4-trihydroxybenzaldehyde was used in place of methoxysalicyaldehyde. The product was isolated as a white solid (3.6 g,

82% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.1 (bs, 3H), 6.58 (d, J = 8 Hz, 1H), 6.47 (d, J = 8 Hz, 1H), 3.75 (s, 2H); m/z 271(M+H).

EXAMPLE 240

[000259] This illustrates the production of 2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000260] 2,3-dihydroxy-4-methoxybenzaldehyde (3 mmol, 506 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 398 mg), acetic acid (1 mL), and ethanol (15 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL) at 0°C. Triethylsilane (25 mmol, 2.88 g, 4 mL) was added via syringe. The reaction stirred for overnight at room temperature to give a yellow slurry. Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (482 mg, 35% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.73 (d, J=8.5 Hz, 1H), 6.57 (d, J=8.5 Hz,1H), 3.77(s, 3H), 3.57 (s, 2H); m/z 285 (M+H); Anal. calculated for $C_{14}H_{12}N_4O_3$-1.25CF_3CO_2H -1.5H_2O: C, 43.58; H, 3.62; N, 12.32, found: C, 43.80; H, 3.22; N, 12.65.

EXAMPLE 241

[000261] This illustrates the production of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000262] 2,3-dihydroxybenzaldehyde (5 mmol, 691 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (5 mmol, 661 mg), acetic acid (1.2 mL), and ethanol (20 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (20 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL) was added via syringe. The reaction stirred for two and one-half days at room temperature to give a solution, which was concentrated *in vacuo*. The residue was stirred in methanol and the slurry was filtered. The product was obtained as a brown solid by concentrating the filtrate (167 mg, 9% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91 (t, J = 7.7 Hz, 1H), 6.86-6.70 (m, 2H), 6.59 (d, J = 7.3 Hz 1H), 3.61 (s, 2H); m/z 255 (M+H).

EXAMPLE 242

[000263] This illustrates the production of 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000264] Step 1: Preparation of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile: 5-nitrosalicylaldehyde (132 mmol, 22.00 g), 2-amino-1-propene-1,1,3-tricarbonitrile (132 mmol, 17.39 g), acetic acid (31 mL), and ethanol (500 mL) were combined and heated to reflux overnight. The resulting slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (350 mL) at 0°C. Triethylsilane (1.40 mol, 162 g, 225 mL) was added. The mixture was heated overnight at 66 °C. The mixture was cooled and concentrated *in vacuo*. Triturating with methanol gave 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a yellow solid (22.48 g, 60%yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (d, J = 9.0 Hz, 1H), 8.00 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 6.70 (br s, 2H), 6.50 (bs, 2H), 3.82 (s, 2H); m/z 284 (M+H); Anal. Calcd for $C_{13}H_9N_5O_3$-0.5H_2O: C, 53.43; H, 3.45; N, 23.96, found: C, 53.41; H, 3.17; N, 23.71.

[000265] Step 2: A mixture of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described above, (0.55 mmol, 155 mg) and palladium on carbon (Pd/C) (35 mg, 10% on activated carbon) in DMF (15 mL) was stirred under an atmosphere of hydrogen (balloon) for 3.5 hours. The catalyst was removed by filtration using a plug of celite. The filtrated was concentrated *in vacuo* and the residue was triturated with methanol to give 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a grey solid (109 mg, 79% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.72 (d, J = 8.0 Hz, 1H), 6.39-6.5(m, 4H), 6.25 (s, 2H), 3.52 (s, 2H); m/z 254 (M+H).

EXAMPLE 243

[000266] This illustrates the production of 2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000267] 3-Fluoro-2-hydroxybenzaldehyde (3.45 mmol, 484 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3.50 mmol, 463 mg), acetic acid (0.9 mL) and ethanol (27 mL) were combined and heated to reflux for 14 hours.

The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10.5 mL). Triethylsilane (43mmol, 4.97 g, 6.9 mL) was added via syringe. The reaction was heated to reflux for 5 hours. Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with methanol. The product was isolated as a white solid (377 mg, 30% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25-7.19 (m, 1H), 7.15-7.08 (m, 1H), 7.00-6.96 (m, 1H), 6.70 (bs, 2H), 6.51 (bs, 2H), 3.75 (S, 2H); m/z 257 (M+H).

EXAMPLE 244.

[000268] This illustrates the production of 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid Bis(trifluoroacetate).

[000269] 5-Carboxysalicyaldehyde (3 mmol, 500 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 396 mg) acetic acid (1.2 mL), and ethanol (15 mL) were combined and heated to reflux for 2.5days. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL). Triethylsilane (62 mmol, 7.2g, 10 mL) was added via syringe. The reaction was stirred for 4 hours at 50 °C and then was stirred overnight at room temperature. Dichloromethane (20 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (560 mg, 36% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.86 (d, J = 7.4 Hz, 1H), 7.85 (s, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.80 (br s, 2H), 3.85 (s, 2H); m/z 283 (M+H); anal. Calculated for $C_{14}H_{10}N_4O_3$-2CF_3CO_2H-0.25H_2O: C, 42.00; H, 2.45; N, 10.88, found: C, 42.30; H, 2.31; N, 10.51.

EXAMPLE 245

[000270] This illustrates the production of 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000271] 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 244, except that 2,4,6-trihydroxybenzaldehyde was used in place of 5-carboxysalicyaldehyde. The product was isolated as an orange solid (106 mg, 9% yield). ^{1}H NMR (free base, 300 MHz, DMSO-d_6): δ 9.65 (s, 1H),

9.40 (s, 1H), 6.41 (s, 2H), 6.35 (s, 2H), 6.10 (s, 1H), 5.85 (s, 1H), 3.31 (s, 2H); m/z 271 (M+H).

EXAMPLES 246 - 264

[000272] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000273] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 242. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	M+H
246	2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	282
247	2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
248	2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	287
249	2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299
250	2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	323
251	2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
252	2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	314
253	2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	253
254	2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	283
255	2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	269

Ex. No.	Compound name	M+H
256	2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351
257	2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
258	2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	284
259	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
260	2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	254
261	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	257
262	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	273
263	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	295
264	ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	311

EXAMPLE 265

[000274] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000275] Step 1: Production of 5-Nitrothiosalicylaldehyde: A mixture of 2-chloro-5-nitrobenzaldehyde (2g, 11 mmol) and lithium sulfide (0.54 g, 11.7 mmol) in 30 mL of anhydrous DMSO was stirred under nitrogen at room temperature overnight. The solution was then added to a mixture of ice-water, acidified with 2N HCl and extracted with ether three times. The combined ether layers were washed with water, brine, dried, filtered and concentrated to give the crude 5-nitro-2-thiosalicylaldehyde as an orange solid (1.3g, 65% yield)

[000276] Step 2: A solution of the crude 5-nitro-2-thiosalicylaldehyde (1.3g, 7.1 mmol), 2-amino-1-propene-1,1,3-tricarbonitrile (7.6 mmol, 1 g), acetic acid (2.5 mL) in 70 mL of ethanol was heated at 76^{0}C under nitrogen overnight. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ethanol to give the desired tricyclic intermediate as a light brown solid (1.5g, 71.4% yield).

[000277] Step 3: A reaction mixture of the aforementioned tricyclic intermediate (1.2 g, 4 mmol) and triethylsilane (15 mL) in 100 mL of trifluoroacetic acid was heated at between 60-65^{0}C under nitrogen for 2 hours. After that, the solution was cooled to room temperature and concentrated in vacuo. Ether was added to the residue. The solid was filtered, washed with additional ether to give 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile as an orange powder (0.9 g, 75% yield). ^{1}H NMR (400 MHz, CD_3CN + D_2O) δ 8.089 (d, 1H), 8.046 (dd, 1H), 7.609 (d, 1H), 3.898 (s, 2H); m/z 300 (M+H).

EXAMPLE 266

[000278] This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000279] To 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (produced as described above in Example 265; 0.8 g, 2.7 mmol) in 9 mL of 50% (by weight) of ethanol-water was added iron powder (0.55 g, 10 mmol). The mixture was heated to 60°C and then 0.5 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76°C for 2.5 hours and filtered hot. The solid was washed with 50% ethanol-water. The filtrates were combined and concentrated *in vacuo* to give a brownish yellow solid. The solid was then dissolved in acetonitrile, filtered to remove a small amount of insoluble solid and concentrated *in vacuo*. The resulting solid was then washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated in vacuo to give an amber oil. Ether was added and the solid was filtered, washed with ether, air-dried overnight and then dried in a vacuum oven at 44°C for 2 hours to

give the product as a grayish solid (0.53 g, 71% yield). ^{1}H NMR (400 MHz, $CD_3CN + D_2O$) δ 7.153 (d, 1H), 6.792 (s, 1H), 6.698 (d, 1H), 3.628 (s, 2H); m/z 270 (M+H).

EXAMPLE 267

[000280] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000281] To a solution of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 265, (3 g, 10 mmol) in 125 mL of trifluoroacetic acid cooled with a water bath was added dropwise 30% hydrogen peroxide (8 g). After addition was completed, the water bath was removed. After 4 hours, additional 30% hydrogen peroxide (2 g) was added and stirring at room temperature was continued for additional 2 hours. After that, water (20 mL) was added and the resulting solution was concentrated to about 70 mL. Then more water was added and the yellow suspension was stirred at room temperature overnight. The suspension was filtered and washed with water to give the desired product as a yellow solid (2 g, 60.4% yield). ^{1}H NMR(400MHz, DMSO + D_2O) δ 8.350 (dd, 1H), 8.265 (d, 1H), 8.220 (d, 1H), 4.160 (s, 2H); m/z 332 (M+H).

EXAMPLE 268

[000282] This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000283] A mixture of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, produced as described in Example 267, (0.8 g, 2.4 mmol) and iron powder (0.58 g, 10 mmol) in 50% of ethanol-water (10 mL) was heated to 70^{0}C, then 1 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76°C for 3 hours and filtered hot. The solid was washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated *in vacuo* and ether was added to the viscous oil. The solid was filtered and washed with ether to give the desired product as a beige solid (0.42 g, 57.5% yield). ^{1}H NMR

(400 MHz, DMSO + D_2O) δ 7.521 (d, 1H), 6.60 (dd, 1H), 6.529 (s, 1H), 3.753 (s, 2H); m/z 302 (M+H).

EXAMPLE 269

[000284] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000285] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared as a bis-trifluoroacetate in the same manner as described in Example 265, except that 2,5-difluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The product was isolated as a beige solid (0.35 g, 35% yield). ^1H NMR (400 MHz, CD_3CN + D_2O) δ 7.425 (dd, 1H), 7.153 (dd, 1 H), 7.088 (dt, 1H) 3.743 (s, 2H); m/z 273 (M+H)

EXAMPLE 270

[000286] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

[000287] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 265, except that 2-fluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The product was isolated as a beige solid (1.8 g, 47.4% yield). ^1H NMR (400 MHz, CD_3CN + D_2O) δ 7.271-7.435 (m, 4H), 3.785 (s, 2 H); m/z 255 (M+H).

EXAMPLE 271

[000288] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000289] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 265, except that 2-fluoro-5-methoxybenzaldehyde was used as the starting material. The product was isolated as a beige solid (0.5 g, 49% yield). ^1H NMR (400 MHz, CD_3CN + D_2O) δ 7.329 (d, 1H), 6.938 (d, 1H), 6.885 (dd, 1H), 3.795 (s, 3H), 3.710 (s, 2H); m/z 285 (M+H)

EXAMPLE 272

[000290] This illustrates the production of 2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000291] A mixture of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.3 g, 0.59 mmol), produced as described in Example 271, and 0.6 mL of boron tribromide (6.4 mmol) in 30 mL of methylene chloride was stirred at room temperature for 18 h. After that, the solid was filtered, washed with methylene chloride, water and methanol. The methanol filtrate was concentrated to give a solid, which was washed with water, acetonitrile and ether to give the desired product as a red solid (54 mg, 33.6% yield). ^{1}H NMR (400 MHz, DMSO + D_2O) δ 9.520 (s, 1H), 8.111 (d, 1H), 7.561 (d, 1H), 7.522 (s, 2H); m/z 271 (M+H).

EXAMPLE 273

[000292] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide (an alternative procedure).

[000293] A mixture of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.1 g, 0.26 mmol), produced as described in Example 268, and 30% hydrogen peroxide (1.5 mL) in 3 mL of trifluoroacetic acid was stirred at room temperature overnight. Water (30 mL) was then added and the resulting suspension was stirred at ambient temperature for 2 hours. The solid was filtered to give the desired product as a yellow solid (18 mg, 8.6% yield): ^{1}H NMR (400 MHz, DMSO + D_2O) δ 8.353 (dd, 1H), 8.263 (d, 1H), 8.228 (d, 1H), 4.163 (s, 2H); m/z 332 (M+H).

EXAMPLE 274

[000294] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000295] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 273. The product was isolated as a yellow solid (51 mg, 32.7% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.028 (q,

1H), 7.433 (dt, 1H), 7.253 (d, 1H), 7.162 (bs, 1H), 6.917 (bs, 1H), 4.024 (s, 2H); m/z 305 (M+H).

EXAMPLE 275.

[000296] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000297] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 273. The product was isolated as a yellow solid (73 mg, 42.9% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.945 (dd, 1H), 7.762 (dt, 1H), 7.568 (t, 1H), 7.467 (d, 2H), 7.179 (bs, 2H), 6.886 (bs, 1H), 4.009 (s, 2H); m/z 287 (M+H).

EXAMPLE 276.

[000298] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000299] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 273. The product was isolated as a light brown solid (110 mg, 34.2% yield). ^{1}H NMR (400 MHz, DMSO + D_2O) δ 7.858 (d, 1H), 7.107 (dd, 1H), 6.972 (d, 1H), 3.942 (2, 2H), 3.833 (s, 3H); m/z 316 (M+H).

EXAMPLES 277 - 278

[000300] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000301] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 273. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	m/z (M+H)
277	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	273
278	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	305

EXAMPLES 279 - 294

[000302] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000303] General procedure for the N-alkylation:

[000304] To a solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34 mmol) and the corresponding halide (2.01 mmol) in dimethylformamide (5 mL) is added sodium hydride (80 mg, 2.01 mmol). The reaction mixture is stirred at room temperature or heated to 40°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography. Both the mono alkylated and dialkylated product were isolated.

[000305] The following compounds were prepared using the procedure described above:

Example 279: 2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 280: 2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 281: 2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 282: 2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 283: 2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 284: 7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 285: 2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate,

Example 286: *N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,

Example 287: 7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 288: 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 289: 2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile

Example 290: 2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 291: 7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 292: 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 293: 2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 294: 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000306] General procedure for the demethylation:

[000307] To a solution of the corresponding dimethoxy aryl analog (0.68 mmol) in dichloromethane (2mL) is slowly added boron tribromide (1M, dichloromethane, 3.38mmol, 3.38mL). The reaction mixture is stirred at room temperature for 4 hours, quenched with 5% aqueous sodium hydroxide, then neutralized with 5% aqueous HCl. The resulting solid is collected and the aqueous layer is extracted with dichloromethane. The organic layer is concentrated under vacuum and combined with the solid. The residue is purified by reverse phase chromatography.

EXAMPLE 295

[000308] This illustrates the production of 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000309] 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above starting with 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(q, 2H), 2.5 (s, 2H), 1.25 (t, 3H); m/z 299.15 (M+H); HRMS (M+H) calculated for $C_{15}H_{15}N_4O_3$ 299.1139, found 299.1113.

EXAMPLE 296

[000310] This illustrates the production of 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000311] 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile is prepared using the demethylation procedure described above for Examples 279 - 294 starting with 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.55(m, 2H), 2.5 (s, 2H), 1.6(m, 2H), 1.35 (t, 3H); m/z 313.16 (M+H); HRMS (M+H) calculated for $C_{16}H_{17}N_4O_3$ 313.1295, found 313.1325.

EXAMPLE 297

[000312] This illustrates the production of 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000313] 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above for Examples 279 - 294, starting with 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(m, 2H), 3.55(m, 2H), 2.5 (s, 2H); m/z 315.13 (M+H).

EXAMPLE 298

[000314] This illustrates the production of 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000315] 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared by using the procedure described in Examples 279 - 294.

EXAMPLES 299 - 304

[000316] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000317] General procedure for the O-alkylation of phenol 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile:

[000318] A solution of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.73 mmol), and powdered sodium hydroxide (117 mg, 2.93 mmol)) in dimethyl sulfoxide (4 mL) is heated to 50°C for five minutes. The corresponding halide is added and the reaction mixture is stirred at 50°C or 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography.

[000319] The following compounds were prepared using the above procedure:

Example 299: 2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 300: (2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,

Example 301: 2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 302: 2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 303: 2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 304: 2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

EXAMPLES 305 - 333

[000320] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000321] General procedure for the Mannich condensation:

[000322] To a solution of the corresponding phenol (0.92 mmol) in ethanol (5 mL) is added formic acid (37% solution, 76 µL, 1.01 mmol) and piperidine (100 µL, 1.01 mmol). The reaction mixture is stirred at 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography and each regioisomer isolated.

[000323] The following compounds were prepared using the above procedure:

Example 305: 2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 306: 2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, were produced starting with 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Examples 299 - 304, and

Example 307: 2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, was produced starting with 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 221.

[000324] Other aminocyanopyridine compounds of the present invention can be produced by the same general method, and are shown in the table below along with NMR parameters, which were determined as described above.

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
308	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1778	$C_{19}H_{21}N_5O_2$
309	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.33	449.266	449.2637	$C_{25}H_{32}N_6O_2$
310	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.32	449.266	449.2629	$C_{25}H_{32}N_6O_2$
311	2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1777	$C_{19}H_{21}N_5O_2$
312	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	346.16	346.1299	346.1344	$C_{19}H_{15}N_5O_2$
313	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326.24	326.1612	326.1607	$C_{17}H_{19}N_5O_2$
314	2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299.19	299.1139	299.1153	$C_{15}H_{14}N_4O_3$
315	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	313.14	313.0931	313.0972	$C_{15}H_{12}N_4O_4$
316	2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	298.18	298.1299	298.1303	$C_{15}H_{15}N_5O_2$

Ex. N .	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
317	2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	327.2	327.1452	327.1493	$C_{17}H_{18}N_4O_3$
318	2-amino-4-{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	370.27	370.1874	370.1869	$C_{19}H_{23}N_5O_3$
319	2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	441.31	441.2609	411.2629	$C_{23}H_{32}N_6O_3$
320	2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	342.22	342.1561	342.1546	$C_{17}H_{19}N_5O_3$
321	2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	472.21			$C_{25}H_{21}N_5O_5$
322	2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	396.32	396.203	396.2061	$C_{21}H_{25}N_5O_3$
323	7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	493.44			$C_{27}H_{36}N_6O_3$
324	2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	415.33			$C_{19}H_{18}N_4O_7$
325	*N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	357.26	357.1193	357.1818	$C_{17}H_{16}N_4O_5$

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
326	7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	415.3	415.1976	415.1972	$C_{21}H_{26}N_4O_5$
327	2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	357.25	357.1557	357.2538	$C_{18}H_{20}N_4O_4$
328	2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	411.35	411.2391	411.2391	$C_{23}H_{30}N_4O_3$
329	2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.26	355.1765	355.1763	$C_{19}H_{22}N_4O_3$
330	7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	383.31	383.2078	383.2085	$C_{21}H_{26}N_4O_3$
331	2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	341.25	341.1608	341.1623	$C_{18}H_{20}N_4O_3$
332	2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.27	355.1765	355.1784	$C_{19}H_{22}N_4O_3$
333	2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	327.21	327.1452	327.142	$C_{17}H_{18}N_4O_3$

EXAMPLE 334

[000325] This illustrates the production of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000326] To a stirred solution of 3,4-dimethoxyphenol (35.7mmol, 5.5g) and piperidine (40mmol, 3.4g) in ethanol (50mL) was slowly added formaldehyde (37%, water, 39.5mmol, 3.2g). The mixture was stirred at room temperature for 4 hours and then evaporated *in vacuo* and the

resultant residue was partitioned between ethyl acetate (100mL) and water (100 mL). The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give a colorless oily residue. To a solution of the above oily product in acetone was added methyl iodide (100mmol, 14.2g) and the mixture was stirred at room temperature overnight. The resultant white precipitate was collected by filtration, washed with ether and air-dried to give 8.14 g of a white solid.

[000327] To a slurry of the above solid (1mmol, 390mg) and 2-amino-1-propene-1,1,3-tricarbonitrile (1mmol, 132mg) in ethanol (10mL) was added triethylamine (0.5mL) and the resultant solution was heated at reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration, washed with ethanol and air-dried to give the product as a white solid (178mg, 60% yield). ^{1}H NMR (400 MHZ, DMSO) δ 6.582 (s, 1H), 6.574 (s, 1H), 6.406 (s, 2H), 6.241 (s, 2H), 3.686 (s, 3H), 3.671 (s, 3H), 3.524 (s, 2H); m/z 299 (M+H).

EXAMPLE 335

[000328] This illustrates the production of 2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000329] To a solution of 2-hydroxy-4-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (250mL) was added six drops of piperidine. The mixture was heated at 50°C for 10 minutes and then stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a pale yellow solid (1.19g, 36% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.274(d, 1H), 6.999 (s, 2H), 6.817 (dd, 1H), 6.733 (d, 1H), 6.619 (s, 2H), 4.804 (d, 1H), 4.734 (d, 1H), 3.757 (s, 3H); m/z 333 (M+H).

EXAMPLE 336

[000330] This illustrates the production of 2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000331] To a solution of 5-bromo-2-hydroxybenzaldehyde (10mmol, 2g) and malononitrile (35mmol, 2.31g) in ethanol (200mL) was added six drops of piperidine and the mixture was stirred at room temperature for 30

hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a white solid (1.68g, 44% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.489 (dd, 1H), 7.344 (d, 1H), 7.230 (d, 1H), 7.063 (s, 2H), 6.686 (s, 2H), 4.876 (d, 1H), 4.850 (d, 1H); m/z 381, 383 (M+H).

EXAMPLE 337

[000332] This illustrates the production of 2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000333] To a solution of 2-hydroxy-5-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 18 hours. The resultant precipitate was collected by filtration, successively washed with ethanol and ether and and air-dried to give the product as a grey solid (1.42g, 43% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.107(d, 1H), 6.990 (m, 3H), 6.865 (d, 1H), 6.603 (s, 2H), 4.850 (d, 1H), 4.794 (d, 1H), 3.724 (s, 3H); m/z 333 (M+H).

EXAMPLE 338

[000334] This illustrates the production of 2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

[000335] To a solution of 2,4-dihydroxybenzaldehyde (10mmol, 1.38g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration, washed successively with ethanol and ether and air-dried to give the product as a yellow solid (1.62g, 51% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.887 (s, 1H), 7.162 (d, 1H), 6.971 (s, 2H), 6.613 (dd, 1H), 6.597 (s, 2H), 6.497 (d, 1H), 4.743 (d, 1H), 4.687 (d, 1H); m/z 319 (M+H).

EXAMPLE 339 - 348

[000336] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

[000337] The aminocyanopyridine compounds listed in the table below were produced according to the general method described in Example

336. NMR analysis was carried out for each material according to the method described above. The names and NMR data for each compound is provided in the table.

Ex. No.	Compound name	m/z (M+H)
339	2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
340	2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	319
341	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	317, 319
342	2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	333
343	2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
344	2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	337
345	2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	331
346	2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
347	2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	347, 349
348	2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	345

EXAMPLE 349

[000338] This example illustrates that MK2 knock-out mice (MK2 (-/-)) are resistant to the formation of K/BN serum-induced arthritis.

[000339] A strain of mice has been reported that develops symptoms similar to human rheumatoid arthritis. The mice were designated K/BxN mice. See, Wipke, B. T. and P. M. Allen, *J. of Immunology, 167:*1601 - 1608 (2001). Serum from the mice can be injected into host animals to provoke a typical RA response. The progression of the RA symptoms in the mice is measured by measuring paw thickness as a function of time.

[000340] In the present example, host mice having normal MK-2 production (MK2 (+/+)) were genetically altered by disabling the gene encoding MK-2 to produce mice having no capability of endogenous synthesis of active MK-2 (MK2 (-/-)). Normal host mice (MK2 (+/+)) and MK-2 knock-out mice (MK2 (-/-), were separated into four groups with each group containing both male and female mice. All groups of mice were treated similarly, except that one group (Normal), composed of MK2 (+/+) mice that served as the control group, was not injected with serum from K/BxN mice, while the other three groups were injected with K/BxN serum at day 0. The other three groups of mice were MK2 (+/+), MK2 (-/-), and Anti-TNF. The Anti-TNF group was composed of MK2 (+/+) mice which were also injected at day) with anti-TNF antibody. The paw thickness of all mice was measured immediately after the injections on day 0, and then on each successive day thereafter for 7 days.

[000341] Figure 1 is a graph that shows paw thickness as a function of time from day 0 to day 7 for MK2 (+/+) and MK2 (-/-) mice, which have received serum injection. It can be seen that paw thickness increased significantly for MK2(+/+) mice, whereas there was substantially no increase in paw thickness for MK2 knock-out mice. This indicated the requirement for a functioning MK2 regulatory system to the inflammatory response caused by the serum challenge. When anti-TNF antibody was administered to the MK2 (+/+) mice along with the serum injection, the swelling response was significantly reduced. This can be seen in Figure 2, which is a bar chart showing paw thickness at seven days after injection for normal mice, MK2 (+/+) mice receiving serum, MK2 (-/-) mice receiving serum, and MK2 (+/+) mice receiving serum and anti-TNF antibody.

[000342] This data shows that the MK2 knock-out mice show no arthritic response to a serum challenge, whereas MK2 (+/+) mice show a normal response. Treatment of MK2 (+/+) mice that receive a serum challenge with anti-TNF antibody reduces the response back to near-normal levels. This illustrates the utility of the MK2 regulatory system as a potential control point for the modulation of TNF production, and indicates that

such regulation could serve as a treatment for inflammation -- such as that caused by arthritis, for example. It further shows that MK2 inhibition can have a beneficial effect on inflammation, and indicates that administration of an MK2 inhibitor can be an effective method of preventing or treating TNF modulated diseases or disorders.

[000343] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000344] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000345] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.